IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 07-731, 08-057, 08-463 (GMS)

IMPAX LABORATORIES, INC.'S MOTION TO TRANSFER

I. INTRODUCTION

Impax respectfully requests the Court to transfer these actions pursuant to 28 U.S.C. § 1404(a) to the District of New Jersey. There, plaintiffs Endo and Penwest are litigating the same two patents against another party for the same allegedly infringing activity – *i.e.*, the filing of an abbreviated new drug application ("ANDA") to market a generic version of Endo's Opana® ER. The transfer will conserve the currently over-burdened judicial resources in the District of Delaware. This Court's lengthy judicial vacancy has over-taxed the resources of this Court, where three judges have been doing the work of four in a district already bearing a heavy caseload of patent lawsuits. First filed more than nine months ago, the actions against Impax have no schedule yet and no Rule 16 case management conference is on the calendar. By contrast, a similar ANDA case in the District of New Jersey filed four months after this case has a claim construction schedule and a final pre-trial conference set for September 2009. Transferring the Delaware actions to New Jersey, a jurisdiction where some of its judges have agreed to sit by designation in Delaware specifically to alleviate the congestion created by the vacant judgeship, makes practical sense. Litigating the same two patents in two courts is wasteful; litigating them in the same court will allow for streamlined discovery and discovery-dispute resolution, coordinated claims construction, and possibly a joint trial, thus eliminating any possibility of inconsistent results. Second to file its ANDA, and second to be sued, the other

generic drug applicant in New Jersey may be able to force Impax to launch its product at risk or face forfeiture of its first-to-file exclusivity by virtue of being in a significantly less-congested court. Justice dictates transferring these cases to New Jersey, where Impax may at least be on the same footing as the later-filed generic drug applicant.

II. BACKGROUND

A. Plaintiffs' complaints against Impax in Delaware.

On November 15, 2007, Endo and Penwest sued Impax in this Court, accusing Impax of infringing U.S. Patent No. 5,662,933 (the "'933 patent") and U.S. Patent No. 5,958,456 (the "'456 patent") by submitting an ANDA to the Food and Drug Administration ("FDA") to market a generic version of Opana® ER (D.I. 1 of Case No. 07-731-GMS) (originally assigned to the vacant judgeship as 07-731-***). Endo and Penwest sued Impax again on the same patents on January 25, 2008 (D.I. 1 of Case No. 08-57-GMS). Then, when Impax notified Endo and Penwest that it had amended its ANDA to include additional strengths, on July 25, 2008, Endo and Penwest sued Impax for a third time on the same patents in this Court (D.I. 1 of Case No. 08-463-GMS).[1] On August 19, 2008, Impax responded to the third action by asserting that the '933 patent is also unenforceable due to inequitable conduct (D.I. 1 of Case No. 08-463-GMS). Nine months after the filing of the first suit, none of these three actions have a schedule or a Rule 16 case management conference on calendar.

B. Plaintiffs' complaints against Actavis in New Jersey.

Four months after they sued Impax, Endo and Penwest sued Actavis on March 28, 2008, in the United States District Court for the District of New Jersey, accusing Actavis of infringing the '456 patent by submitting an ANDA to the FDA to market a generic version of Opana® ER. *See* Ex. A, Complaint For Patent Infringement, Case No. 08-1563. On May 5, 2008, Actavis asserted counterclaims, which among other things, seek a declaratory judgment that its ANDA does not infringe the '933 patent and that the '933 patent is invalid and unenforceable. *See* Ex.

[1] The three Delaware actions, Case Nos. 07-731-GMS, 08-57-GMS, and 08-463-GMS, are collectively referred to herein as the "Delaware Actions."

B, Defendant Actavis South Atlantic LLC's Answer and Counterclaims. On June 11, 2008, the United States District Court for the District of New Jersey entered a scheduling order, setting a final pretrial conference date of September 8, 2009. *See* Ex. C, Pretrial Scheduling Order.

After Actavis notified Endo and Penwest that it had amended its ANDA to include additional dosages, on July 11, 2008, Endo and Penwest sued Actavis for a second time in the United States District Court for the District of New Jersey, accusing Actavis of infringing the '456 patent by submitting its amended ANDA to the FDA. *See* Ex. D, Complaint For Patent Infringement, Case No. 08-3482.[2] On August 14, 2008, Actavis asserted counterclaims, which among other things, seek a declaratory judgment that its ANDA does not infringe the '933 patent and that the '933 patent is invalid and unenforceable. *See* Ex. E, Defendant Actavis South Atlantic LLC's Answer, Separate Defenses, Counterclaims and Demand For Jury Trial. On August 15, 2008, the court in New Jersey consolidated the New Jersey Actions in order to "avoid duplication and conserve the resources of the parties and the Court." *See* Ex. F, Order on Informal Application & Amended Pretrial Scheduling Order.

III. ARGUMENT

Under 28 U.S.C. § 1404(a), the Court may transfer the three actions before this Court "for the convenience of the parties and witnesses, in the interest of justice … to any other district … where it might have been brought." In deciding this issue, the Court must determine "whether on balance the litigation would more conveniently proceed and the interest of justice be better served by transfer to a different forum." *Bank of America, N.A. v. S.I.P. Assets, LLC*, C.A. No. 07-159-GMS, 2007 U.S. Dist. LEXIS 67107, **4-5 (D. Del. Sept. 11, 2007) (quoting *Jumara v. State Farm Ins. Co.*, 55 F.3d 873, 879 (3d Cir. 1995)). This balancing test includes public interest and private interest factors.[3] *Id.*

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[2] The two New Jersey actions, Case Nos. 08-1563 and 08-3482, are collectively referred to herein as the "New Jersey Actions."

[3] Public interest factors include "the enforceability of the judgment; practical considerations that could make the trial easy, expeditious, or inexpensive; the relative administrative difficulty in the two fora resulting from court congestion; the local interest in deciding local controversies at home; [and] the public policies of the fora." *Bank of America, N.A.*, 2007 U.S. Dist. LEXIS

The prerequisite that the case be transferred to a district where it might have been brought is satisfied because Endo and Penwest could have brought this action in New Jersey. Impax is subject to personal jurisdiction in New Jersey. 28 U.S.C. § 1391(c); 28 U.S.C. § 1400(b).

A. A transfer of the Delaware Actions to New Jersey is in the interest of justice.

The interest of justice is "[t]he most significant criterion for deciding a motion to transfer...." *Chrysler Capital Corp. v. Woehling*, 663 F. Supp. 478, 483 (D. Del. 1987). Here, through no fault of the parties or the Court, there is an extremely unusual situation creating delay, which will not rectify until after this delay has prejudiced Impax. Transferring the Delaware Actions to New Jersey serves the interest of justice because (1) congestion in this Court makes litigation in New Jersey more practical, (2) a transfer will conserve judicial resources, and (3) Impax will likely suffer prejudice if the New Jersey Actions proceed without it.

1. Transferring the Delaware Actions will relieve some court congestion in Delaware.

The consideration of "the relative administrative difficulty in the two fora resulting from court congestion" weighs in favor of transferring these actions to New Jersey. *See Bank of America*, 2007 U.S. Dist. LEXIS 67107, *5; *see also Omnicom Group, Inc. v. Employers Reinsurance Corp.*, C.A. No. 01-839-GMS, 2002 U.S. Dist. LEXIS 1275, *11 (D. Del. Jan. 28, 2002) (relative caseloads a factor in transfer analysis); *Mona Industries, Inc. v. Philip A. Hunt Chemical Corp.*, No. 4628, 1973 U.S. Dist. LEXIS 11368, *4 (D. Del. Oct. 25, 1973) ("The court calendar is a recognized factor to be considered in weighing a transfer motion."). As this Court is well aware, the continued vacancy of one of this Court's four judgeships has created a backlog of cases that the Court has taken various approaches to address. Most recently, on July 28, 2008, the Third Circuit issued orders allowing six judges from other districts to take on cases within the District of Delaware. This Court's backlog has stalled the proceedings in the

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67107, *4. Private interest factors include "the plaintiff's choice of forum; the defendant's preference; whether the claim arose elsewhere; the convenience of the parties; the convenience of the expected witnesses; and the location of the books and records, to the extent that they could not be produced in the alternative forum." *Id.*

Delaware Actions—no deadlines are set in any of the actions. Meanwhile, the New Jersey court demonstrably has the capacity for a nearly identical patent litigation, as evidenced by the fact that the later-filed New Jersey Actions already have a schedule through the pretrial conference. This current motion, which seeks to transfer to another court within the Third Circuit, similarly would assist in addressing the Court's backlog.

2. A transfer to New Jersey will conserve judicial resources.

a. The Delaware Actions and New Jersey Actions significantly overlap.

The issues in the Delaware Actions significantly overlap with the issues in the New Jersey Actions: infringement and invalidity of the '456 and '933 patents, and unenforceability of the '933 patent are at issue in both forums. Because most issues overlap, a transfer of the Delaware Actions to New Jersey will promote judicial efficiency. The defendants jointly could conduct discovery, reducing their burdens as well as the burden on plaintiffs. A single court could handle discovery disputes. Moreover, rather than conducting *Markman* procedures in two different forums on the same patents, the parties could conduct a single *Markman* hearing (opening *Markman* briefs are currently due November 24, 2008 in the first New Jersey action). The New Jersey court could also consider motions for summary judgment simultaneously and possibly even conduct a joint trial. Finally, having a single court oversee litigations involving the same issues eliminates the possibility of inconsistent results.

b. Substantial precedent exists for transferring patent actions when there is overlap with issues in a pending action in another forum.

Even though a plaintiff's choice of forum is normally given deference, this Court and others have transferred pending patent actions when the same issues are being litigated in another forum to conserve judicial resources.

This Court transferred a patent infringement action to the Middle District of Florida when the plaintiff's claims in this Court mirrored the first two affirmative defenses of one of the defendant's answers in the Florida action because "allowing both cases to proceed concurrently would be both inconvenient to the parties and an inefficient use of judicial resources." *Bank of*

America, N.A., 2007 U.S. Dist. LEXIS 67107, *7. Similarly, this Court transferred a patent infringement action to the Western District of Washington when the same parties were concurrently litigating the infringement of a third patent there. *See Brunswick Corp. v. Precor Inc.*, C.A. No. 00-691-GMS, 2000 U.S. Dist. LEXIS 22222 (D. Del. Dec. 12, 2000); *see also Chrysler Capital Corp*, 663 F. Supp. at 483 ("suits involving the same legal and factual issues should be decided by one court and not permitted to proceed in two different courts").

This Court even transferred a first-filed patent infringement action to federal court in Missouri because the action had little connection with Delaware and "because the parties are litigating apparently related issues in Missouri, travel time and convenience in the aggregate would be substantially increased with a transfer of forum." *Bayer Bioscience N.V. v. Monsanto Co.*, C.A. No. 03-023-GMS, 2003 U.S. Dist. LEXIS 4594, *6 (D. Del. Mar. 25, 2003). Likewise, this Court transferred a first-filed patent infringement for consolidation with a later-filed action in California "because the parties are already litigating essentially the same issues in California." *Allergan, Inc. v. Alcon Labs., Inc.*, C.A. No. 02-1682-GMS, 2003 U.S. Dist. LEXIS 2564, *5 (D. Del. Feb. 25, 2003).

Courts also transfer actions in patent litigation under the Federal Food, Drug, and Cosmetic Act when a related action is taking place in another forum. When a plaintiff filed two actions in two different forums alleging that the submission of an ANDA infringed its patent, the court in the first-filed action transferred that action to the other forum because the second-filed action was "already underway," had a scheduled trial date, and "[i]t is in the interests of judicial economy to avoid a duplication of efforts and to have these two lawsuits consolidated into one action." *Bristol-Myers Squibb Co. v. Andrx Phram., LLC*, 03 Civ. 2503 (SHS), 2003 U.S. Dist. LEXIS 21967, *16-17 (S.D.N.Y. Dec. 5, 2003); *see also Aventis Pharma S.A. v. Sandoz Inc.*, C.A. No. 06-3671 (MLC), 2007 U.S. Dist. LEXIS 26304 (D.N.J. Apr. 10, 2007) (granting plaintiffs' motion to transfer to forum with same claims and counterclaims pending).

This case thus is similar to other cases in which this Court and others have transferred to another forum. Indeed, this Court's current congestion makes the case an even more attractive candidate for transfer.

3. Transferring the Delaware Actions will reduce possible prejudice to Impax.

The Court should transfer the three Delaware actions because, without a transfer, Impax may be prejudiced. According to the FDA, Impax has first-to-file exclusivity on the original strengths of Opana® ER (or generically called, oxymorphone hydrochloride extended release tablets). *See* FDA's Paragraph IV Patent Certifications <http://www.fda.gov/cder/ogd/ppiv.htm> (last checked Sept. 5, 2008). On these original strengths, Actavis is a second filer – which typically means that Actavis has to stay off the market until Impax's first-to file (or 180-day) exclusivity expires. *See* 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb). In this instance, however, Actavis may try to make Impax forfeit its first-to-file benefits under the first-to-file forfeiture provisions (that is, trigger the clock on forfeiture) by virtue of being in a significantly less congested court. *See* 21 U.S.C. § 355(j)(5)(D). That possibility could be avoided if the Delaware actions were transferred to New Jersey, where Impax could at least be on equal footing with the second filer, Actavis.

B. New Jersey is a more convenient forum than Delaware for the parties and witnesses.

"The transfer of a case will generally be regarded as less inconvenient to a plaintiff if the plaintiff has not chosen … a forum where the alleged wrongful activity occurred." *Brunswick Corp.*, 2000 U.S. Dist. LEXIS 22222, *7 (quoting *Continental Casualty Co. v. American Home Assurance Co.*, 61 F. Supp. 2d 128, 131 (D. Del. 1999)). This is true even if one or more of the parties is incorporated in Delaware. *See Bayer Bioscience N.V.*, 2003 U.S. Dist. LEXIS 4594; *Allergen, Inc.*, 2003 U.S. Dist. LEXIS 2564. In the actions before this Court, none of the relevant acts took place in Delaware, none of these parties have a principle place of business in Delaware and there is little connection between this action and the state. Impax's ANDA, which is alleged to infringe, was developed primarily in California, and Penwest's work on the patents-in-suit presumably took place near where the named inventors were located, which is New York

and Connecticut. Moreover, Endo and Penwest themselves have selected the court in New Jersey to litigate these patents, so they cannot argue that transferring these actions to New Jersey would cause them any inconvenience whatsoever. In fact, it would actually reduce costs and eliminate duplication of efforts. Therefore, New Jersey is at least as convenient as–if not more convenient than–Delaware for the parties and witnesses.

IV. CONCLUSION

For the reasons stated above, this Court should transfer the three actions pending before it to the United States District Court for the District of New Jersey.

Mary B. Matterer #2696
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19801-1494
(302) 888-6800
mmatterer@morrisjames.com

Asim Bhansali
Klaus H. Hamm
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111
(415) 391-5400

Attorneys for Defendant
Impax Laboratories, Inc.

Dated: September 5, 2008

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 07-731, 08-057, 08-463 (GMS)

[PROPOSED] ORDER

WHEREAS, the Court having considered Impax Laboratories, Inc.'s Motion to Transfer;

IT IS HEREBY ORDERED this ____ day of _____, 2008 that the Motion is GRANTED.

_____
U.S. District Court Judge

IN THE UNITED STATES DISTRICT COURT
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EXHIBITS A-C IN SUPPORT OF IMPAX LABORATORIES, INC.'S MOTION TO TRANSFER

Mary B. Matterer #2696
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19801-1494
(302) 888-6800
mmatterer@morrisjames.com

Asim Bhansali
Klaus H. Hamm
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111
(415) 391-5400

Attorneys for Defendant Impax Laboratories, Inc.

Dated: September 5, 2008

EXHIBIT A

Robert D. Rhoad
Thomas P. Lihan
DECHERT LLP
A Pennsylvania Limited Liability Partnership
Princeton Pike Corporate Center
P.O. Box 5218
Princeton, NJ 08543-5218
(609) 620-3200
ATTORNEYS FOR *Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.*

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	
ACTAVIS SOUTH ATLANTIC LLC,	)	
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest"), for their Complaint against defendant Actavis South Atlantic LLC ("Actavis"), allege as follows.

PARTIES

1. Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceutical company engaged in the research, development, sale and marketing of prescription pharmaceuticals used primarily to treat and manage pain, including OPANA® ER.

2. Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. Penwest is a drug development company focused primarily on the identification, development and commercialization of products for diseases of the nervous system using its expertise in drug development and drug delivery technology, including the extended-release technology used in OPANA® ER.

3. Upon information and belief, Actavis is a limited liability company, organized and existing under the laws of the State of Delaware, having its principal place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325.

4. Upon information and belief, Actavis is in the business of manufacturing generic drug products for sale and use throughout the United States, including in this judicial district.

NATURE OF ACTION

5. This is an action for infringement of United States Patent No. 5,958,456 ("the '456 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

7. This Court has jurisdiction over Actavis, for among other reasons, Actavis has continuous and systematic contacts within this judicial district and Actavis directly, or

through its divisions, subsidiaries, parent, agents and/or alter-egos maintains executive offices and a manufacturing facility in this judicial district.

FACTUAL BACKGROUND

8. On September 28, 1999, the PTO duly and legally issued the '456 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. A true and correct copy of the '456 patent is attached as Exhibit A.

9. Penwest is the assignee and owner of the '456 patent, and Endo is an exclusive licensee of this patent in the relevant field of use pursuant to a strategic alliance agreement with Penwest.

10. On June 22, 2006, the United States Food and Drug Administration (the "FDA") approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which contain oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

11. On October 19, 2007, Endo submitted information regarding the '456 patent to the FDA for listing in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book"), with respect to OPANA® ER tablets. The FDA thereafter listed the '456 patent in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

12. Upon information and belief, Actavis has submitted to the FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of oxymorphone hydrochloride extended-

release tablets as generic versions of OPANA® ER tablets. Upon information and belief, this ANDA submission has been designated as ANDA No. 79-046.

13. On or about February 12, 2008, Actavis sent Penwest and Endo a notice stating that it had submitted an ANDA seeking approval to manufacture, use, or sell generic oxymorphone hydrochloride extended-release tablets prior to the expiration of the '456 patent (the "Actavis Notice").

14. The Actavis Notice advised Penwest and Endo that Actavis' ANDA included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "paragraph IV certification") that, in Actavis' opinion, the claims of the '456 patent are invalid and/or that the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '456 patent.

COUNT I

INFRINGEMENT OF THE '456 PATENT

15. Plaintiffs incorporate each of the preceding paragraphs 1 to 14 as if fully set forth herein.

16. Actavis' submission of an ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations of which it first notified plaintiffs on February 12, 2008, constitutes infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A).

17. Actavis' commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '456 patent.

18. Upon information and belief, Actavis was aware of the existence of the '456 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the

filing of its Paragraph IV Certification with respect to the '456 patent constitutes infringement of that patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Actavis has infringed the '456 patent;

B. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Actavis' ANDA No. 79-046 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), shall not be earlier than the expiration date of the '456 patent, including any extensions;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Actavis, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '456 patent for the full terms thereof, including any extensions; and

D. Costs and expenses in this action; and

E. Such other and further relief as the Court may deem just and proper.

DECHERT LLP

s/ Robert D. Rhoad

Robert D. Rhoad
Thomas P. Lihan
P. O. Box 5218
Princeton, NJ 08543-5218
(609) 620-3200

Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Of Counsel:

Martin J. Black
George G. Gordon
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808
(215) 994-4000

Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Ann M. Caviani Pease
DECHERT LLP
2440 W. El Camino Real
Suite 700
Mountain View, CA 94040-1499
(650) 813-4800

Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

March 28, 2008

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify to the best of my knowledge, information and belief that the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Date: March 28, 2008

By: s/ Robert D. Rhoad
Robert D. Rhoad

EXHIBIT A

US005958456A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,958,456

[45] Date of Patent: *Sep. 28, 1999

[54] CONTROLLED RELEASE FORMULATION (ALBUTEROL)

[75] Inventors: Anand Baichwal, Wappingers Falls, N.Y.; Troy W. McCall, New Milford, Conn.

[73] Assignee: Edward Mendell Co., Inc., Patterson, N.Y.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 08/886,496

[22] Filed: Jul. 1, 1997

Related U.S. Application Data

[63] Continuation of application No. 08/553,008, Nov. 3, 1995, Pat. No. 5,662,933, which is a continuation-in-part of application No. 08/118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] Int. Cl.[6] A61K 9/14

[52] U.S. Cl. 424/489; 424/488; 424/457; 424/468

[58] Field of Search 424/489, 488, 424/457, 468

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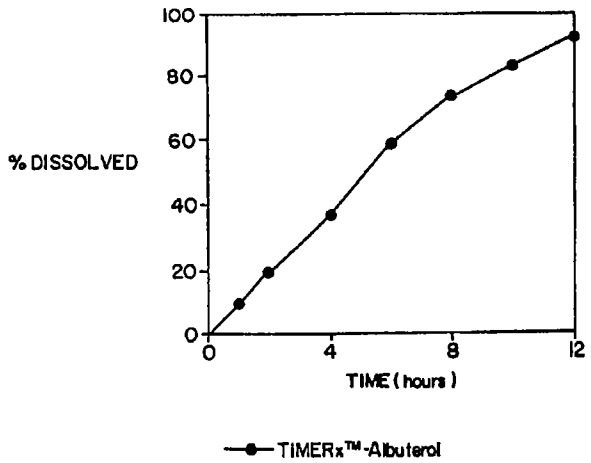
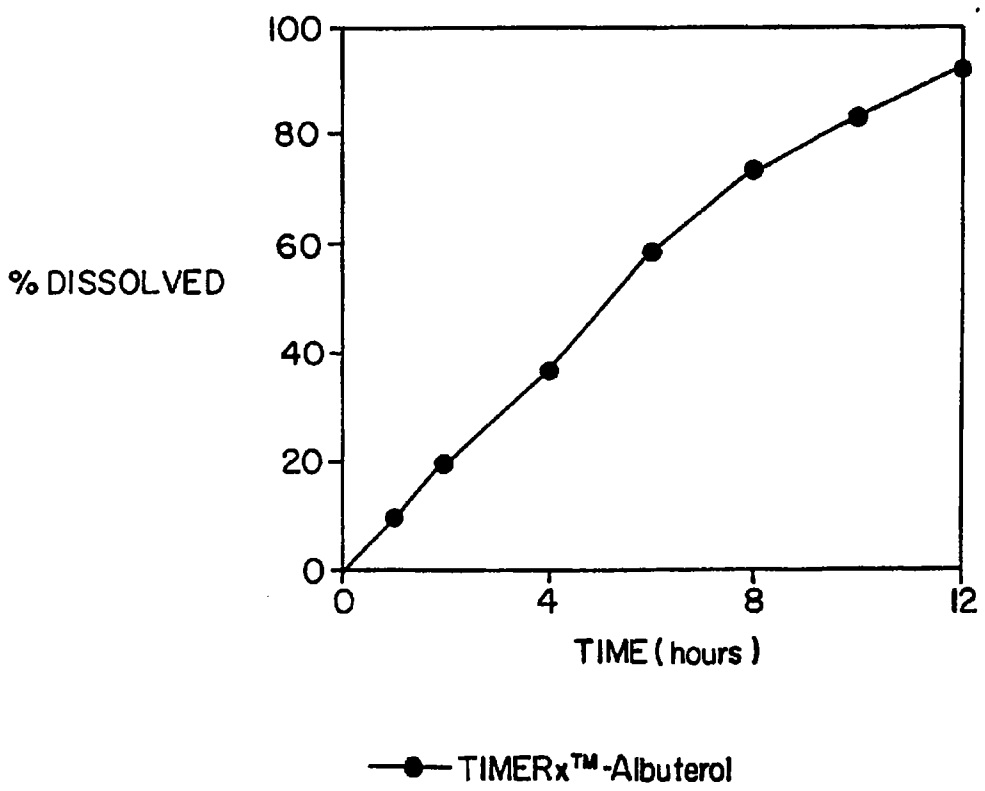
Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Davidson,Davidson & Kappel,LLC

[57] ABSTRACT

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

16 Claims, 3 Drawing Sheets




% DISSOLVED
100
80
60
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20
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4
8
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TIME (hours)
TIMERx™-Albuterol

FIG. 1

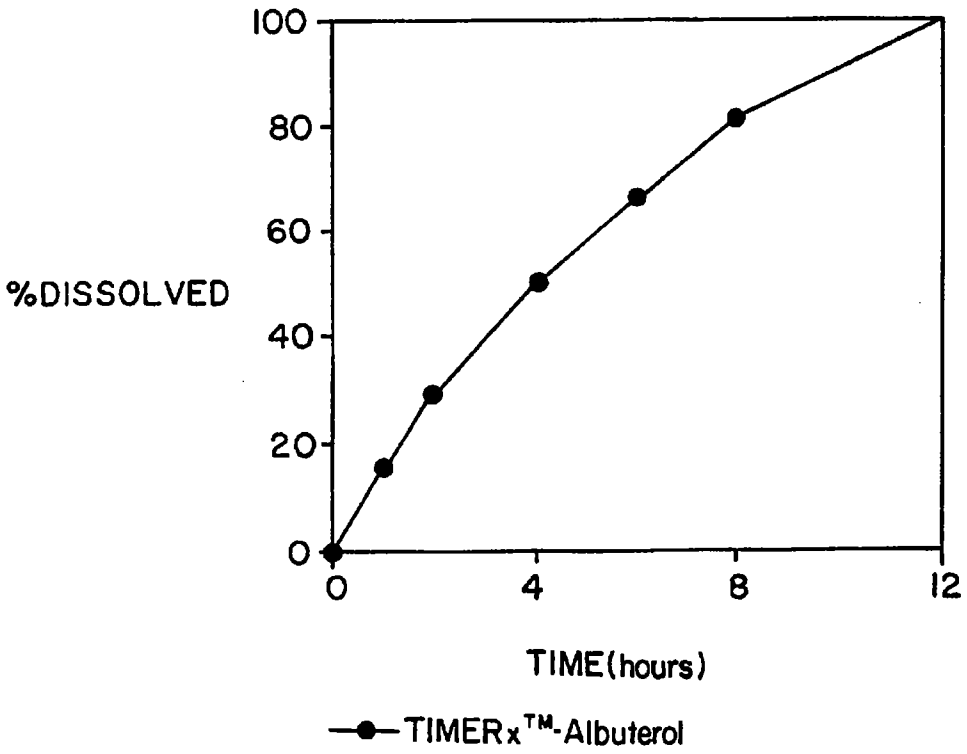
100
80
60
40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

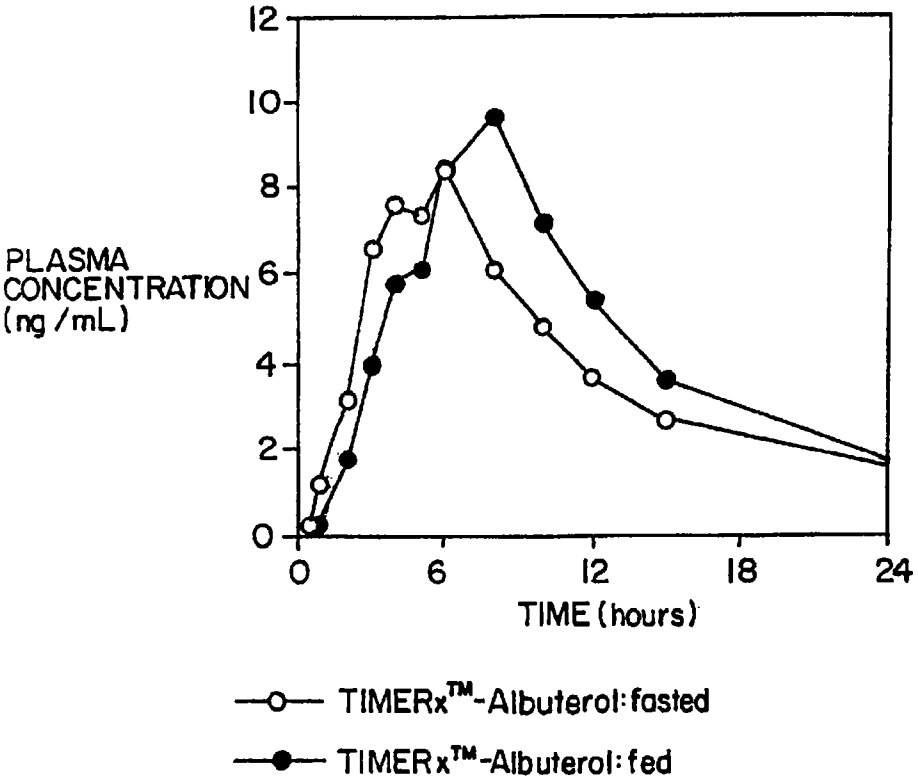
PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 08/553,008, filed Nov. 3, 1995, now U.S. Pat. No. 5,662,933, which is a continuation-in-part of Ser. No. 08/118,924, filed Sep. 9, 1993, now U.S. Pat. No. 5,455,046.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_∞"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_∞ ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_∞ (fasting patient) to AUC_∞ (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, Iowa 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g, 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diurctics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead or the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2-selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such

pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and time$_{\Delta}$ to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt (mg)	334.6	204.7
Diameter (in)	⅛	⅛
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

	Component	Example 3	Example 4
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	CAP	10	30
4.	Dextrose	60	40
5.	Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

	Component	Example 3	Examples 4
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

Time (hrs)	Example 3	Example 4
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

	Component	Example 5	Example 6
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	PVAP	10	30
4.	Dextrose	60	40
5.	Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

	Component	Example 5	Example 6
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

Time (hrs)	Example 5	Example 6
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean

gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

	Component	Example 7	Example 8
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	HPMCP	10	30
4.	Dextrose	60	40
5.	Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

	Component	Example 7	Example 8
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

	Example 7	Example 8
Time (hrs)		
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	63.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

	Component	Excipient for Examples 9–12
1.	Xanthan gum	12%
2.	Locust bean gum	18
3.	Dextrose	65
4.	EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ®, from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250, 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

	Component	Percent
1.	SRE*	8.2%
2.	Albuterol sulfate	5.3
3.	Polyvinyl acetate phthalate	5.0
4.	Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	⅜			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0–1 hr pH 1.5 1–2 hr pH 3.5 2–4 hr pH 5.5 4–12 hr pH 7.5	30% peanut oil
Agitation:	15 cpm	15 cpm
Volume:	250 mL	250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

Results and Discussion

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 though 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max}, and AUC_{28} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter	TIMERx fasted	TIMERx fed
Cmax		
mean	10.5	10.6
% CV	39.0	31.0
Tmax		
mean	4.5	7.0
% CV	29.0	23.0
AUCInf		
mean	113.4	128.1
% CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted:TIMERx fed	0.98	0.64	0.89
TIMERx fed:TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

Conclusion

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various

modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent; a pharmaceutically acceptable hydrophobic material; and an inert pharmaceutical diluent wherein the ratio of said inert diluent to said gelling agent is from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The controlled release solid dosage form according to claim 1 wherein said inert diluent is selected from the group consisting of pharmaceutically acceptable saccharides, polyhydric alcohols, pre-manufactured direct compression diluents, and mixtures of any of the foregoing.

3. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

4. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

5. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25 percent to about 50 percent, by weight, of the solid dosage form.

6. The controlled release solid dosage form according to claim 1, wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

7. The controlled release solid dosage form according to claim 1 which is a tablet.

8. The controlled release solid dosage form according to claim 1, which is in granulate form.

9. The controlled release solid dosage form according to claim 8, wherein said granulate is coated with a hydrophobic material to a weight gain from about 1 percent to about 20 percent.

10. The controlled release solid dosage form according to claim 1, wherein the medicament comprises an amount of albuterol equivalent to about 4 mg to about 16 mg of albuterol free base.

11. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing of a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to about 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding a therapeutically effective amount of a medicament to said excipient, such that

a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

12. The method of claim 11, further comprising compressing said mixture of said sustained release excipient and said medicament into tablets.

13. The method of claim 11, wherein said medicament is albuterol or a salt or derivative thereof.

14. The method of claim 13, further comprising coating the resultant tablets with a hydrophobic coating to a weight gain from about 1 percent to about 20 percent.

15. A method of treating a patient with albuterol comprising:

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of albuterol or a salt or derivative thereof to said sustained release excipient, tableting the resultant mixture into tablets such that said tablets have a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol for at least 12 hours; and

administering said tablet to a patient on a once-a-day or twice-a-day basis.

16. The method of claim 15, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

* * * * *

EXHIBIT B

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
SAIBER LLC
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Tracey B. Davies (tdavies@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
Erin A. Thomson (ethomson@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

Attorneys for Defendant and Counterclaim Plaintiff
Actavis South Atlantic LLC

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. ACTAVIS SOUTH ATLANTIC LLC, Defendant.	**Civil Action No. 08-1563 (KSH) (PS)** ***Document Electronically Filed***

DEFENDANT ACTAVIS SOUTH ATLANTIC LLC'S ANSWER AND COUNTERCLAIMS

Defendant Actavis South Atlantic LLC ("ASA"), by its attorneys, responds to the averments made in the numbered paragraphs of the Complaint filed by Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest") as follows:

1. On information and belief, ASA admits that Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317, and that Endo sells OPANA® ER. ASA is without specific knowledge or information sufficient to form a belief as to the remaining allegations in this paragraph and, on that basis, denies them.

2. On information and belief, ASA admits that Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. ASA is without specific knowledge or information sufficient to form a belief as to the remaining allegations in this paragraph and, on that basis, denies them.

3. ASA admits the allegations in paragraph 3 therein.

4. ASA admits that it manufactures generic drug products for sale and use in the United States and in this district, but denies the remaining allegations in paragraph 4 therein.

5. ASA admits that Plaintiff purports to assert an action for infringement of U.S. Patent No. 5,958,456 ("the '456 patent") and that Plaintiff's claim for patent infringement purports to arise under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, but denies the remaining allegations in paragraph 5 therein.

6. ASA admits the allegations in paragraph 6 therein.

7. ASA admits that jurisdiction in this district is proper, but denies the remaining allegations in paragraph 7 therein.

8. ASA admits that the '456 patent, entitled "Controlled Release Formulation (Albuterol)", purports on its face to have been issued by the United States Patent and Trademark Office ("USPTO") on September 28, 1999 to Edward Mendell Co., Inc. as the

named assignee and admits that a copy of the '456 patent was attached as Exhibit A as alleged in paragraph 8, but denies the remaining allegations therein.

9. ASA is without specific knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 9 therein and, on that basis, denies them.

10. On information and belief, ASA admits that New Drug Application ("NDA") No. 21-610 for OPANA® ER tablets was approved on June 22, 2006, as alleged in paragraph 10, but avers that the NDA speaks for itself with respect to its contents. ASA denies the remaining allegations therein.

11. ASA admits that the Food and Drug Administration ("FDA") has listed the '456 patent in its publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") as alleged in paragraph 11, but ASA is without specific knowledge or information sufficient to form a belief as to the truth of the remaining allegations therein and, on that basis, denies them.

12. ASA admits that it filed Abbreviated New Drug Application ("ANDA") No. 79-046 with the FDA under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacturing, use or sale of oxymorphone hydrochloride extended release tablets as alleged in paragraph 12, but denies the remaining allegations therein.

13. ASA admits the allegations in paragraph 13 therein.

14. ASA admits the allegations in paragraph 14 therein.

RESPONSE TO COUNT I
(Alleged Infringement of the '456 Patent)

15. ASA reasserts and incorporates by reference each of the answers to paragraphs 1-14 above, as if fully set forth herein.

16. ASA denies the allegations in paragraph 16 therein.

17. ASA denies the allegations in paragraph 17 therein.

18. ASA admits that the Paragraph IV certification in its ANDA references the '456 patent as alleged in paragraph 18, but denies the remaining allegations therein.

SEPARATE DEFENSES

Without any admission as to the burden of proof or as to any of the averments in the Complaint, ASA sets forth the following defenses:

FIRST SEPARATE DEFENSE

19. ASA has not infringed any claim of the '456 patent, either literally or under the doctrine of equivalents.

SECOND SEPARATE DEFENSE

20. ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 will not infringe any claim of the '456 patent, either literally or under the doctrine of equivalents.

THIRD SEPARATE DEFENSE

21. Plaintiff is barred by 35 U.S.C. § 288 from recovering any costs associated with this suit.

FOURTH SEPARATE DEFENSE

22. The claims of the '456 patent are invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

FIFTH SEPARATE DEFENSE

23. The claims of the '456 patent are invalid under the judicially created doctrine of non-statutory, obviousness-type double patenting.

SIXTH SEPARATE DEFENSE

24. The doctrine of prosecution history estoppel precludes a finding that ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 would infringe the claims of the '456 patent by equivalence.

SEVENTH SEPARATE DEFENSE

25. The claims of the '456 patent will not be not infringed by ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 under the doctrine of equivalents because all embodiments described in prior patents in the '456 patent family and/or in the '456 patent but not claimed by them are dedicated to the public.

EIGHTH SEPARATE DEFENSE

26. The claims of the '456 patent are unenforceable due to inequitable conduct committed during prosecution of the '456 patent and/or prior patents in the same patent family.

27. On its face, the '456 patent was filed as U.S. Pat. App. No. 08/866,496 ("the '496 application") and purports to be a continuation of U.S. Pat. App. No. 08/553,008 ("the '008 application"), issued as U.S. Pat. No. 5,662,933 ("the '933 patent").

28. The '933 patent, in turn, purports to be a continuation-in-part of U.S. Pat. App. No. 08/118,924 ("the '924 application"), issued as U.S. Pat. No. 5,455,046 ("the '046 patent").

29. On information and belief, the '924, '008 and '496 applications were assigned to Edward Mendell Co., Inc. ("Mendell") during their prosecution. On information and belief, Mendell was renamed Penwest Pharmaceuticals Co. on October 20, 1997.

30. The same attorney prosecuted the '924, '008 and '496 applications.

31. On information and belief, the issue notification for the '924 application was mailed on August 28, 1995 to the attorney prosecuting the '924 application. The '924 application — the purported grandparent application of the '456 patent — issued as the '046 patent on October 3, 1995.

32. The '008 application — the purported parent application of the '456 patent — was filed on November 3, 1995, one month after the '046 patent issued, by the same attorney that paid the issue fee in the '924 application.

33. Despite a lack of co-pendency between the '924 and '008 applications, Mendell nevertheless included the following reference to the '924 application in the '008 specification when the '008 application was filed: "The present application is a continuation-in-part of U.S. application serial number 08/118,924, filed on September 9, 1993[.]" The issuance of and the patent number for the '046 patent were not included in the specification upon filing.

34. As part of the initial filing of the '008 application on November 3, 1995, Mendell filed an unsigned declaration with the '008 application. That declaration contained a claim of priority to Application Serial No. 07/781,980, an unrelated application, and did not contain a priority claim to the '924 application, which had issued as the '046 patent as of the filing date of the '008 application.

35. Mendell subsequently filed a signed declaration for the '008 application on January 16, 1996. This declaration did not contain a claim of priority. The priority claim to Application Serial No. 07/781,980 (the unrelated application) was deleted in this declaration.

36. The issue fee in the '008 application was paid on March 26, 1997.

37. On June 17, 1997, after payment of the issue fee and, on information and belief, without any additional correspondence from the USPTO, Mendell filed a third "Supplemental Declaration."

38. This Supplemental Declaration included a claim of priority to the '924 application and noted that the '924 application was "[p]atented as U.S. 5,455,046." This Supplemental Declaration was filed by the same attorney that paid the issue fee in the '924 application and filed the '008 application. The substantive content of the Supplemental Declaration did not differ in any way from the declaration filed on January 16, 1996, except that the priority claim to the '924 application was added.

39. Despite its awareness of the issuance of the '046 patent as evidenced by the inclusion of the patent number in the Supplemental Declaration, Mendell did not inform the USPTO of the lack of co-pendency prior to the issuance of the '933 patent.

40. Additionally, Mendel never informed the USPTO of the lack of co-pendency during the prosecution of the application that became the '456 patent, even though it also contains an alleged claim of priority to the '046 patent.

41. In sum, despite a lack of co-pendency as required under 35 U.S.C. § 120, Mendell intentionally misrepresented to the USPTO its entitlement to the benefit of the earlier filing date of the '924 application when it filed the '008 application (which issued as the '933 patent and is the purported parent of the '456 patent asserted in this case) with a priority claim to the '924 application.

42. Mendell again intentionally misrepresented its entitlement to the filing date of the '924 application when it filed the application issuing as the '456 patent.

43. Entitlement to an earlier priority date is inherently material to patentability as a matter of law.

44. In light of the intentional misrepresentations of entitlement to priority during the prosecution of the applications that issued as the '933 and '456 patents, the '456 patent is unenforceable due to inequitable conduct.

NINTH SEPARATE DEFENSE

45. ASA repeats and incorporates by reference paragraphs 26 through 44 herein.

46. In addition to misrepresenting its entitlement to an earlier priority date, Mendell also intentionally failed to disclose to the USPTO numerous references that are highly material to the patentability of the claims of the '933 and '456 patents.

47. The '496 application, which issued as the '456 patent, was filed in the names of Anand Baichwal ("Baichwal") and Troy W. McCall ("McCall"). Baichwal and McCall assigned the '496 application to Mendell, which was later renamed Penwest. On information and belief, Baichwal is currently the Senior Vice President of Licensing and Chief Scientific Officer of Penwest.

48. Baichwal is a named inventor on, and Penwest is the assignee of, at least seven patents covering subject matter similar to the subject matter of the claims of the '046, '933 and '456 patents that were not disclosed to the USPTO during prosecution. The non-disclosed Baichwal patents assigned to Penwest include at least: U.S. Pat. Nos. 5,169,639; 5,330,761; 5,399,358; 5,399,359; 5,399,362; 5,472,711; and 5,478,574.

49. The assistant patent examiners indicated on the face of these seven patents are different than the assistant examiners indicated on the face of the '046, '933 and '456 patents.

50. These seven patents are highly material to the patentability of the claims of the '933 and '456 patents.

51. For example, in one instance during prosecution of the application which became the '046 patent, the USPTO rejected the pending, non-withdrawn claims over two patents related to one of the non-disclosed patents, namely U.S. Pat. No. 5,169,639 ("the '639 patent").

52. The '639 patent is a continuation-in-part of U.S. Pat. No. 5,128,143 ("the '143 patent"), which is a continuation-in-part of U.S. Pat. No. 4,994,276 ("the '276 patent"). On information and belief, the '639 patent was prosecuted by the same attorney that prosecuted the '924 application. The '639 patent issued before the '924 application was filed.

53. During prosecution of the '924 application, the USPTO rejected all of the pending, non-withdrawn claims of the '924 application for statutory and non-statutory, obviousness-type double patenting over claims 1-24 of the '143 patent, the parent of the '639 patent.

54. In that same office action, the USPTO rejected all of the pending, non-withdrawn claims of the '924 application for statutory and non-statutory, obviousness-type double patenting over claims 1-18 of U.S. Patent No. 4,994,276 (the grandparent of the '639 patent), which lists Baichwal as an inventor and which was assigned to Penwest.

55. Despite receiving these statutory and non-statutory, obviousness-type double patenting rejections over the '143 and '276 patents, Baichwal and Mendel did not disclose the existence of the '639 patent (the child and grandchild of the '143 and '276 patents) to the USPTO during prosecution of the '924, '008, or '496 applications.

56. In sum, after receiving double patenting rejections over Baichwal patents related to the subject matter of the '924, '496 or '008 applications, Baichwal and Mendel (now Penwest) never disclosed to the USPTO the existence of at least seven other Baichwal patents related to similar subject matter.

57. Additionally, at least two of the non-disclosed Baichwal patents anticipate one or more claims of the '933 and '456 patents, and thus, these patents are highly material to patentability.

58. For example, the '639 patent and U.S. Pat. No. 5,330,761, another one of the at least seven, non-disclosed Baichwal patents, are prior art to the '933 and '456 patents under section 102(b), and both of the patents anticipate one or more of the claims of the '933 and '456 patents because the '933 and '456 patents are not entitled to claim priority to the '046 patent. Thus, these patents are highly material to patentability.

59. In light of the foregoing, the claims of the '456 patent are unenforceable because of inequitable conduct committed during the prosecution of the '924 and '008 applications and again during prosecution of the application issuing as the '456 patent.

COUNTERCLAIMS

ASA, by way of Counterclaim against Plaintiffs, Endo and Penwest, alleges as follows:

1. This is an action for a declaratory judgment of non-infringement, invalidity, and/or unenforceability of the one or more claims of United States Patent Nos. 5,128,143, 5,662,933, 5,958,456, and 7,276,250 ("the '250 patent), under 35 U.S.C. § 271(e)(5), 28 U.S.C. §§ 2201(a) and (b), and 21 U.S.C. § 355(j); and for unfair competition under the common law of the State of New Jersey.

The Parties

2. ASA is a limited liability corporation organized under the laws of the State of Delaware, having a principal place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325.

3. On information and belief, Counterclaim Defendant Penwest is a corporation organized under the laws of the State of Washington, having a principal place of business at 39 Old Ridgebury Road, Suite #11, Danbury, Connecticut 06810.

4. On information and belief, Counterclaim Defendant Endo is a corporation organized under the laws of the State of Delaware, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317.

Jurisdiction

5. This court has subject matter jurisdiction over these Counterclaims for declaratory judgment pursuant to 35 U.S.C. § 271(e)(5); 28 U.S.C. §§ 1331, 1337(a), 1338(a) and (b), 2201(a) and (b); and 21 U.S.C. § 355(j), based on an actual controversy between ASA and counterclaim-defendants arising under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* This court has supplemental jurisdiction over ASA's state law claims pursuant to 28 U.S.C. § 1367

6. This court has personal jurisdiction over Endo and Penwest based, *inter alia*, on the filing by Endo and Penwest of this lawsuit in this jurisdiction.

7. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c), and 1400(b).

Orange Book Listing of the '143, '933, '456, and '250 Patents

8. On information and belief, Penwest is the assignee of the '143, '933, '456, and '250 patents.

9. On information and belief, Penwest has exclusively licensed the '143, '933, '456, and '250 patents to Endo for the manufacture and sale of Endo's oxymorphone hydrochloride extended release drug product, marketed under the name OPANA® ER.

10. On information and belief, pursuant to 21 U.S.C. § 355(b)(1)(G), Endo and/or Penwest caused the FDA to publish the '143, '933, '456 and '250 patents in the Orange Book in connection with NDA No. 02-1610 for OPANA® ER ("the OPANA® ER NDA").

11. Endo and/or Penwest submitted information regarding the '933 and '456 patents to the FDA for publication in the Orange Book in violation of the time requirements for the submission of patent information set forth in 21 C.F.R. § 314.53.

12. Endo and/or Penwest late listed the '933 and '456 patents in the Orange Book after becoming aware of the filing of an ANDA for oxymorphone hydrochloride extended release tablets by Impax Laboratories, Inc. with the intent of delaying the approval of any and all ANDAs for oxymorphone hydrochloride extended release tablets.

13. Endo and/or Penwest late listed the '933 and '456 patents in the Orange Book because they knew that the '143 and '250 patents could not be asserted against Impax, and thus, the listing of the '933 and '456 patents in the Orange Book was designed to manufacture a 30-month stay of approval of Impax's ANDA and delay approval of any subsequent ANDAs.

14. By maintaining the listing of these patents in the Orange Book, Endo represents that the '143, '933, '456, and '250 patents "could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1)(G).

ASA's Abbreviated New Drug Application

15. On June 8, 2007, ASA filed ANDA No. 79-046 ("the ASA ANDA") with the FDA seeking approval to market its proposed oxymorphone hydrochloride extended release tablets in 20 mg and 40 mg strengths. On June 13, 2007 ASA filed an amendment to the ASA ANDA seeking approval to market and sell 5 and 10 mg strength oxymorphone hydrochloride extended release tablets (all strengths collectively referred to as "ASA's oxymorphone products").

16. The FDA thereafter accepted the ASA ANDA for filing.

17. As part of its ANDA filing, ASA certified to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification"), that the manufacture, use and/or sale of ASA's oxymorphone products will not infringe the claims of the '143, '933, '456 and '250 patents and/or that the claims of those patents are invalid.

18. On February 12, 2008, in accordance with the requirements of 21 U.S.C. § 355(j)(2)(B), ASA mailed Penwest and Endo notice letters that it had filed the ASA ANDA containing a Paragraph IV certification regarding the '143, '933, '456 and '250 patents.

19. ASA's notice letters provided a detailed statement of the factual and legal basis establishing that the claims of the '143, '933, '456 and '250 patents are invalid and/or will not be infringed by the manufacture, use or sale of ASA's oxymorphone products.

20. As part of ASA's notice letters to Penwest and Endo, and in accordance with the requirements of 21 U.S.C. § 355(j)(5)(C)(i), ASA offered Penwest and Endo confidential access to the ASA ANDA.

21. Penwest and Endo received the notice letters no later than February 15, 2008.

The Presence of a Case or Controversy

22. By maintaining the Orange Book listing of the '143, '933, '456 and '250 patents in connection with the OPANA® ER NDA, Penwest and its exclusive licensee, Endo, continue to represent that the '143, '933, '456 and '250 patents could reasonably be asserted against anyone making, using or selling a generic extended release oxymorphone hydrochloride product without a license from Penwest.

23. Penwest and Endo have issued joint press releases stating their intent "to pursue all available legal and regulatory avenues in defense of OPANA ER, including enforcement of their intellectual property rights and approved labeling."

24. ASA's Paragraph IV certification states that ASA's oxymorphone products do not infringe any claim of the '143, '933, '456 and '250 patents and/or that the claims of those patents are invalid.

25. In response to ASA's ANDA filing and Paragraph IV certification against all four Orange Book listed patents, Penwest and Endo filed an infringement action under 35 U.S.C. § 271(e)(2)(A) selectively asserting only the '456 patent, thus gaining the exclusionary benefit of an automatic 30-month stay of approval of ASA's ANDA while jeopardizing only the '456 patent in litigation.

26. The statutory 45-day period following Endo and Penwest's receipt of the notice letter expired on March 31, 2008, and neither Endo nor Penwest has asserted the '143, '933, or the '250 patents against ASA.

27. 35 U.S.C. § 271(e)(5) provides that the Court shall have subject matter jurisdiction under 28 U.S.C. § 2201 for a declaratory judgment claim that an Orange Book listed patent that is not asserted during the statutory 45-day period is invalid and/or not infringed.

28. On information and belief, Penwest has asserted the '933 and '456 patents in a similar infringement action against another ANDA filer, Impax Laboratories, Inc., in connection with Impax's ANDA seeking approval to market an extended release oxymorphone hydrochloride product, styled *Endo Pharmaceuticals Inc. v. Impax Laboratories, Inc.*, C.A. No. 08-057, D. Del.

29. Should ASA prevail in this litigation with Penwest and Endo asserting only the '456 patent, ASA would still be faced with the threat of litigation from Penwest and Endo over the three remaining Orange Book listed patents, all relating to the same controversy of the instant '456 action — ASA's ANDA filing and the ASA oxymorphone products.

30. Additionally, if ASA succeeds in proving that ASA has not infringed and that ASA's oxymorphone products will not infringe the '143, '933, '456 or '250 patents and/or that those patents are invalid, such a judgment will remove any independent barriers to competition that may exist by virtue of Penwest and/or Endo's maintenance of the listing of these patents in the Orange Book in connection with the OPANA® ER NDA.

31. In light of all the circumstances, an actual substantial and continuing justifiable controversy having sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Penwest and ASA as to whether the claims of the '143, '933, '456 and '250 patents are invalid and/or not infringed by ASA.

FIRST COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,128,143)

32. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

33. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a

declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 1 of the '143 patent.

34. ASA's oxymorphone products do not contain "xanthan gum and a galactomannan gum capable of cross-linking said xanthan gum in the presence of aqueous solutions" or any equivalent thereto.

35. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 1 of the '143 patent.

36. Further, ASA's oxymorphone products will not infringe at least claim 1 of the '143 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone products infringe by equivalence.

37. Thus, ASA is entitled to a declaratory judgment that ASA has not infringed and ASA's oxymorphone products will not infringe at least claim 1 of the '143 patent.

SECOND COUNT
(Declaratory Judgment of Invalidity, United States Patent No. 5,662,933)

38. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

39. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the invalidity of at least claim 6 of the '933 patent.

40. At least claim 6 of the '933 patent is invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

41. Thus, ASA is entitled to a declaratory judgment that at least claim 6 of the '933 patent is invalid.

THIRD COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,662,933)

42. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

43. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 9 of the '933 patent.

44. ASA's oxymorphone products do not contain "albuterol or a salt or derivative thereof" or any equivalent thereto.

45. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 9 of the '933 patent.

46. Further, ASA's oxymorphone products will not infringe at least claim 9 of the '933 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone products infringe by equivalence.

47. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone products will not infringe at least claim 9 of the '933 patent.

FOURTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,662,933)

48. ASA repeats and incorporates by reference paragraphs 26 through 44 of ASA's Answer and Separate Defenses to the Complaint.

49. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '933 patent.

50. Penwest procured the '933 patent through inequitable conduct by intentionally misrepresenting entitlement to priority, which is inherently material to patentability, to the '046 patent.

51. Thus, ASA is entitled to a declaratory judgment that the '933 patent is unenforceable due to inequitable conduct committed during the prosecution of the '933 patent.

FIFTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,662,933)

52. ASA repeats and incorporates by reference paragraphs 45 through 59 of ASA's Answer and Separate Defenses to the Complaint.

53. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '933 patent.

54. Penwest procured the '933 patent through inequitable conduct by intentionally withholding material prior art from the PTO during the prosecution of the '046, the '933 and the '456 patents.

55. Thus, ASA is entitled to a declaratory judgment that the '933 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent and/or the '046 and '933 patents.

SIXTH COUNT
(Declaratory Judgment of Invalidity, United States Patent No. 5,958,456)

56. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

57. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the invalidity of the claims of the '456 patent.

58. The claims of the '456 patent are invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

59. Thus, ASA is entitled to a declaratory judgment that the claims of the '456 patent are invalid.

SEVENTH COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,958,456)

60. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

61. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of the claims of the '456 patent.

62. ASA has not infringed and ASA's oxymorphone product will not literally infringe any claim of the '456 patent.

63. Further, ASA's oxymorphone product will not infringe any claim of the '456 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone product infringes by equivalence.

64. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone product will not infringe any claim of the '456 patent.

EIGHTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,958,456)

65. ASA repeats and incorporates by reference paragraphs 26 through 44 of ASA's Answer and Separate Defenses to the Complaint.

66. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '456 patent.

67. Penwest procured the '456 patent through inequitable conduct by intentionally misrepresenting entitlement to priority, which is inherently material to patentability, to the '046 patent.

68. Thus, ASA is entitled to a declaratory judgment that the '456 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent.

NINTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,958,456)

69. ASA repeats and incorporates by reference paragraphs 45 through 59 of ASA's Answer and Separate Defenses to the Complaint.

70. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a

declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '456 patent.

71. Penwest procured the '456 patent through inequitable conduct by intentionally withholding material prior art from the PTO during the prosecution of the '046, '933 and '456 patents.

72. Thus, ASA is entitled to a declaratory judgment that the '456 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent and/or the '046 and '933 patents.

TENTH COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 7,276,250)

73. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

74. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 1 of the '250 patent.

75. ASA's oxymorphone products do not contain "about 8.3% to about 41.7% by weight locust bean gum" or an equivalent thereto.

76. ASA's oxymorphone products do not contain "about 8.3% to about 41.7% by weight xanthan gum" or an equivalent thereto.

77. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 1 of the '250 patent.

78. Further, ASA's oxymorphone product will not infringe any claim of the '250 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone product infringe by equivalence.

79. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone product will not infringe at least claim 1 of the '250 patent.

ELEVENTH COUNT
(Unfair Competition under New Jersey Common Law)

80. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses herein and of its foregoing Counterclaims herein.

81. On information and belief, Penwest has exclusively licensed the '143, '933, '456, and '250 patents to Endo for the manufacture and sale of OPANA® ER.

82. On information and belief, Penwest and Endo have joined together in the manufacture and sale of OPANA® ER and the enforcement of the '933 and '456 patents.

83. Penwest and Endo have issued joint press releases stating their intent "to pursue all available legal and regulatory avenues in defense of OPANA ER, including enforcement of their intellectual property rights and approved labeling."

84. OPANA® ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

85. The active pharmaceutical ingredient in OPANA® ER is oxymorphone hydrochloride.

86. Prescriptions written for oxymorphone hydrochloride extended release tablets can be filled only with oxymorphone hydrochloride extended release tablets.

87. At all relevant times, Penwest and Endo have sold substantial amounts of their oxymorphone hydrochloride extended release tablets throughout the United States and particularly in New Jersey.

88. Upon final approval from the FDA, ASA's oxymorphone hydrochloride extended release tablets will be substitutable for, and in direct competition with, Endo's OPANA® ER.

89. Upon final approval from the FDA, ASA plans to sell its oxymorphone hydrochloride extended release tablets throughout the United States and particularly in New Jersey.

90. However, Penwest and Endo are currently the only permitted suppliers of oxymorphone hydrochloride extended release tablets.

91. As set forth with particularity in paragraphs 26 through 59 of ASA's Answer and Separate Defenses to the Complaint herein and as further alleged herein, Penwest and Endo have engaged in unlawful acts, practices and/or policies that constitute unfair competition and/or unfair methods of competition, in violation of the common law of the state of New Jersey. Such acts, practices and/or policies, which are unfair, immoral, unconscionable, and contrary to fair play and respectable business practices, include:

A. Knowingly and fraudulently procuring the '933 and '456 patents;

B. Fraudulently listing the '933 and '456 patents in the Orange Book knowing the claims of said patents to be invalid and unenforceable;

C. Late listing the '933 and '456 patents in the Orange Book in connection with the OPANA® ER NDA in violation of 21 C.F.R. § 314.53 with the intention of delaying the approval of ANDA applications, including ASA's ANDA No. 79-046; and

D. Knowingly and willfully misrepresenting their entitlement to the filing date of an earlier application and failing to disclose highly material references to the PTO examiner, in turn causing the PTO to issue the '933 and '456 patents in reliance on their fraudulent conduct.

92. Penwest and Endo's commercially unfair and wrongful conduct adversely affects the competitive conditions for the sale of oxymorphone hydrochloride extended release tablets by preventing the sale of oxymorphone hydrochloride extended release tablets by other potential suppliers such as ASA, thereby enabling Penwest and Endo to unlawfully and unfairly limit the supply thereof.

93. As a direct result of Penwest and Endo's unfair and injurious conduct, ASA has been prevented from offering oxymorphone hydrochloride extended release tablets for sale.

94. Penwest and Endo's unfair conduct has caused and/or will cause the FDA to delay approval of ASA's ANDA.

95. Similarly, as a direct result of Penwest and Endo's unfair and injurious conduct, consumers have been precluded from benefiting by fair competition between and among suppliers of oxymorphone hydrochloride extended release tablets.

96. Penwest and Endo, unfairly and in bad faith, have acted in opposition to the principles of honesty and fair dealing, the rules of fair play and good conscience, and the morality of the marketplace, and as such committed the commercially immoral acts complained of herein in violation of the common law of unfair competition of the State of New Jersey.

97. As a result, Penwest and Endo are unfairly able to extract artificially high prices for OPANA® ER without competition and without any fear of losing sales to competing products.

98. Penwest and Endo's conduct, which unfairly affected competition in selling oxymorphone hydrochloride extended release tablets, has caused irreparable damage and injury to ASA, and will continue to cause such injury unless Penwest and Endo's actions are enjoined. In response to Penwest and Endo's commercially immoral conduct which constitutes unfair competition and/or unfair methods of competition in violation of the common law of the state of New Jersey, ASA is entitled to preliminary and permanent injunctive relief, declaratory relief, and recovery of monetary damages.

PRAYER FOR RELIEF

WHEREFORE, ASA demands judgment in its favor and against Endo and Penwest as follows:

A. Granting ASA judgment in its favor on Plaintiff's Complaint;

B. Denying Penwest and Endo's request for injunctive relief;

C. Dismissing Penwest and Endo's Complaint with prejudice;

D. Declaring that claim 1 of the '143 patent is not and will not be infringed by ASA;

E. Declaring that claim 6 of the '933 patent is invalid;

F. Declaring that claim 6 of the '933 patent is not and will not be infringed by ASA;

G. Declaring that the claims of the'456 patent are invalid;

H. Declaring that the claims of the '456 patent are not and will not be infringed by ASA;

I. Declaring that claim 1 of the '250 patent is not and will not be infringed by ASA;

J. Declaring the claims of the '933 patent to be unenforceable;

K. Declaring the claims of the '456 patent to be unenforceable;

L. Finding this case to be exceptional under 35 U.S.C. § 285 and awarding ASA its costs and reasonable attorneys' fees;

M. Entering preliminary and permanent injunctions prohibiting Penwest and Endo from engaging in unfair competition and/or unfair methods of competition, including the acts complained of herein;

N. Directing an accounting to determine any and all of Penwest and Endo's profits and ASA's losses resulting from Penwest and Endo's activities and that any such losses be paid over to ASA and increased as the Court finds to be just under the circumstances of this case;

O. Awarding ASA compensatory damages for its injuries caused by Penwest and Endo's unfair competition and/or unfair methods of competition;

P. Disgorging Penwest and Endo's profits collected due to their unfair competition and/or unfair methods of competition;

Q. Awarding ASA punitive damages due to Penwest and Endo's unfair competition and/or unfair methods of competition;

R. Awarding ASA its costs and reasonable attorneys' fees due to Penwest and Endo's unfair competition and/or unfair methods of competition; and

S. Awarding any other such relief as is just and proper.

Respectfully submitted,

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: May 5, 2008

By: /s/ Arnold B. Calmann

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Tracey B. Davies (tdavies@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
Erin A. Thomson (ethomson@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

LOCAL CIVIL RULE 11.2 CERTIFICATION

Under Local Civil Rule 11.2, the undersigned counsel for ASA hereby certifies that this matter is not the subject of any other action asserted by ASA in any court, or of any pending arbitration or administrative proceeding.

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: May 5, 2008

By: /s/ Arnold B. Calmann
Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Tracey B. Davies (tdavies@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
Erin A. Thomson (ethomson@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

LOCAL CIVIL RULE 201.1 CERTIFICATION

Under Local Civil Rule 201.1, the undersigned counsel for ASA hereby certifies that ASA seeks declaratory relief, and therefore this action is not appropriate for compulsory arbitration.

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: May 5, 2008

By: /s/ Arnold B. Calmann
Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Tracey B. Davies (tdavies@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
Erin A. Thomson (ethomson@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

EXHIBIT C

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC.,	
Plaintiff,	**Civil Action No. 08-1563(KSH)**
v.	
ACTAVIS SOUTH,	**PRETRIAL SCHEDULING ORDER**
Defendant	

THIS MATTER having come before the Court for a scheduling conference on the record pursuant to Rule 16 of the Federal Rules of Civil Procedure on June 9, 2008; and for good cause shown,

IT IS on this 9th day of June, 2008,

ORDERED THAT:

1. The parties shall submit a discovery confidentiality order and certification as required by Local Civ. R. 5.3 no later than **June 30, 2008;**

2. The request for leave to file a motion to dismiss in lieu of a response to the counterclaim directed at the '143 patent is denied as moot as the obligation to respond to this portion of the counterclaim is stayed until September 22, 2008. If the patent expires on or before that date, then the parties shall submit a letter and proposed form of Order to the United States District Judge dismissing as moot this portion of the counterclaim. Nothing herein precludes discovery about the '143 patent;

3. The request for leave to file a motion to dismiss the unfair competition counterclaim based upon standing and preemption is granted. Said motion shall be filed no later than **June 13, 2008**. Any response shall be submitted no later than **June 23, 2008** and any reply shall be submitted no later than **June 30, 2008**. The return date shall be **July 7, 2008** before the Hon. Katharine S. Hayden. Her Honor's Chambers will advise the parties if oral argument will be required. Nothing herein precludes discovery on this counterclaim nor does it constitute a ruling on the merits.;

4. The plaintiff shall file a response to the other portions of the Counterclaim no later than **June 13, 2008;**

5. No proceedings, including discovery, will be stayed while dispositive motions or Markman issues are pending;

6. No later than **June 30, 2008**, the plaintiffs shall identify the claims of the '456 patent that they contend the defendant infringes;

7. No later than **July 20, 2008**, the plaintiffs shall provide the factual basis for their assertion that the defendant infringes the identified claims of the patent;

8. No later than **July 20, 2008**, the defendant shall provide the factual basis for its assertion that the '456, 933, and '920 patents are invalid, including citations to prior art;

9. No later than **October 3, 2008**, the parties shall exchange proposed claims terms and claims construction;

10. No later than **October 30, 2008,** the parties shall submit their joint claims construction chart;

11. Opening Markman briefs shall be submitted no later than **November 24, 2008**. Responsive Markman briefs shall be submitted no later than **December 18, 2008**. Judge Hayden shall advise the parties if she seeks a tutorial or needs oral argument.

IT IS FURTHER ORDERED THAT:

I. COURT DATES

1. There shall be telephone status conferences as follows:

Date of Call	Party to Initiate
August 14, 2008 at 1:00 p.m.	**Plaintiff**
October 29, 2008 at 1:00 p.m.	**Defendant**
January 13, 2009 at 1:00 p.m.	**Plaintiff**
April 14, 2009 at 1:00 p.m.	**Defendant**

2. There will be a settlement conference before the undersigned on **TO BE SET**. **Five (5) business days** before the conference, each party should submit a confidential memorandum to the Court, not to exceed 5 pages, summarizing the relevant facts, the respective legal positions, status of the case, and the client's position on settlement. Trial Counsel and clients with full settlement authority must attend the conference. If the trial counsel **and** client with full settlement authority do not appear, the settlement conference may be cancelled or rescheduled and the noncompliant party and/or attorney may be sanctioned, which may include an assessment of the costs and expenses incurred by those parties who appeared as directed.

3. A final pretrial conference shall be conducted pursuant to Fed. R. Civ. P. 16(d) on **September, 8, 2009 at 10:00 a.m.** The Final Pretrial Conference will occur even if there are dispositive motions pending. The Court will adjourn the Final Pretrial conference only if the

requesting party makes a compelling showing that manifest injustice would otherwise result absent adjournment.

II. DISCOVERY AND MOTION PRACTICE

4. Fed. R. Civ. P. 26 disclosures are to be exchanged on or before **completed.**

5. Discovery necessary to engage in meaningful settlement discussions: **none.**

6. A. The parties may serve interrogatories limited to **25** single questions including subparts and requests for production of documents on or before **June 20, 2008,** which shall be responded to no later than **July 20, 2008.**

B. Foreign evidence collection shall commence no later than **July 31, 2008.**

C. Final supplemental responses to contention interrogatories shall be provided no later than **February 8, 2009. Additional supplementation may also be made no later than ten business days after the date of the Order resolving claims construction;**

7. The number of depositions to be taken by each side shall not exceed **10**. No objections to questions posed at depositions shall be made other than as to lack of foundation, form or privilege. See Fed. R. Civ. P. 32(d) (3) (A). No instruction not to answer shall be given unless a privilege is implicated. The depositions shall be completed no later than **March 1, 2009**.

8. Fact discovery is to remain open through **March 1, 2009**. No discovery is to be issued or engaged in beyond that date, except upon application and for good cause shown.

9. Counsel shall confer in a good faith attempt to informally resolve any discovery disputes before seeking the Court's intervention. Should such informal effort fail to resolve the dispute, the matter shall be brought to the Court's attention via a joint letter that sets forth: (a) the request, (b) the response; (c) efforts to resolve the dispute; (d) why the complaining party believes the information is relevant and why the responding party's response continues to be deficient; and (e) why the responding party believes the response is sufficient. No further submissions regarding the dispute may be submitted without leave of Court. If necessary, the Court will thereafter schedule a telephone conference to resolve the dispute.

No discovery motion or motion for sanctions for failure to provide discovery shall be made before utilizing the procedures set forth in these paragraphs without prior leave of Court.

Any unresolved discovery disputes (other than those that arise during depositions) must be brought before the Court no later than **November 10, 2008** and the Court will not entertain applications concerning discovery matters, informally or otherwise, after this date.

10. Any motion to amend pleadings or join parties must be filed by **December 1, 2008.**

11 All dispositive motions shall be discussed in advance of filing with the undersigned either in person or by teleconference.

If leave is granted to file a summary judgment motion, the following protocol shall apply:

a. Each motion for summary judgment shall be supported by a separate, short, and concise statement of material facts, set forth in numbered paragraphs, as to which the moving party contends there is no genuine issue of material fact to be tried. Each fact asserted in the statement shall be supported by a record citation. A "record citation" is a citation to a specific page or paragraph of identified record material supporting the assertion.

b. Each response in opposition shall be accompanied by a separate, short, and concise statement of material facts. The opposing statement shall admit, deny or qualify the facts by reference to each numbered paragraph of the moving party's statement of material facts and unless a fact is admitted, shall support each denial or qualification by a record citation. The opposing statement may contain in a separate section additional facts, set forth in separate numbered paragraphs and supported by a record citation.

c. In the event a party seeks to submit a reply, the party shall file a formal request for permission to do so within the time period provided by Local Rule, attaching the proposed reply. Accompanying the proposed reply shall be a separate, short, and concise statement of material facts which shall be limited to any additional facts submitted by the opposing party. The reply statement shall admit, deny or qualify such additional facts by reference to the numbered paragraphs of the opposing party's statement of material facts, and unless a fact is admitted, shall support each denial or qualification by a record citation.

d. Facts contained in a supporting or opposing statement of material facts, if supported by record citations, shall be deemed admitted unless properly controverted. The Court may disregard any statement of fact not supported by a specific citation to record material properly considered on summary judgment. The Court shall have no independent duty to search or consider any part of the record not specifically referenced in the parties' separate statement of facts.

e. Local Rules governing electronic filing and length, font-size, and format of moving, opposing and reply briefs shall continue to apply as appropriate. Parties shall provide the Court with two hard copies of all submissions by delivering same to the Clerk's Office, Attention Judge Katharine Hayden.

III. EXPERTS

12. All affirmative expert reports shall be delivered by **May 1, 2009.**

13. All responding expert reports shall be delivered by **June 30, 2009**.

14. a. All expert reports are to be in the form and content as required by Fed. R. Civ. P. 26(a) (2)(B). No expert shall testify at trial as to any opinions or base those opinions on facts not substantially disclosed in the experts report.

b. All expert depositions shall be completed by **July 30, 2009**.

IV. FINAL PRETRIAL CONFERENCE

15. A final pretrial conference shall be conducted pursuant to Fed. R. Civ. P. 16(d) on **September, 8, 2009 at 10:00 a.m.**. The Final Pretrial Conference will occur even if there are dispositive motions pending. The Court will adjourn the Final Pretrial conference only if the

requesting party makes a compelling showing that manifest injustice would otherwise result absent adjournment.

16. Not later than **20 working days** before the pretrial conference, the parties shall exchange copies of all proposed trial exhibits. Each exhibit shall be pre-marked with an exhibit number conforming to the party's exhibit list.

17. All counsel are directed to assemble at the office of Plaintiff's counsel not later than **ten (10) days** before the pretrial conference to prepare the proposed Joint Final Pretrial Order in the form and content required by the Court. Plaintiff's counsel shall prepare the Joint Pretrial Order and shall submit it to all other counsel for approval and execution.

18. With respect to non-jury trials, each party shall submit to the District Judge and to opposing counsel proposed Findings of Fact and Conclusions of Law, trial briefs and any hypothetical questions to be put to an expert witness on direct examination.

19. The original joint proposed final pretrial order shall be delivered to the CHAMBERS of the undersigned no later than **September 1, 2009 at 4:00 p.m**. All counsel are responsible for the timely submission of the Order.

20. The Court expects to engage in meaningful settlement discussions at the final pretrial conference. Therefore, trial counsel who actually has full settlement authority must attend the conference and clients or other persons with full settlement authority must be available by telephone.

V. MISCELLANEOUS

21. The Court may from time to time schedule conferences as may be required, either sua sponte or at the request of a party.

22. Since all dates set forth herein are established with the assistance and knowledge of counsel, there will be no extensions except for good cause shown and by leave of Court, even with consent of all counsel.

23. A copy of every pleading, document or written communication with the Court shall be served on all other parties to the action. Any such communication which does not recite or contain a certification of such service may be disregarded by the Court.

24. Communications to the Court by facsimile will not be accepted. All communications to the Court shall be in writing or by telephone conference.

25. **FAILURE TO COMPLY WITH THE TERMS OF THIS ORDER MAY RESULT IN SANCTIONS.**

s/Patty Shwartz
UNITED STATES MAGISTRATE JUDGE

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 07-731, 08-057, 08-463 (GMS)

EXHIBITS D-F IN SUPPORT OF IMPAX LABORATORIES, INC.'S MOTION TO TRANSFER

Mary B. Matterer #2696
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19801-1494
(302) 888-6800
mmatterer@morrisjames.com

Asim Bhansali
Klaus H. Hamm
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111
(415) 391-5400

Attorneys for Defendant
Impax Laboratories, Inc.

Dated: September 5, 2008

EXHIBIT D

Robert D. Rhoad
Thomas P. Lihan
DECHERT LLP
A Pennsylvania Limited Liability Partnership
902 Carnegie Center, Suite 500
Princeton, NJ 08540
(609) 955-3200
ATTORNEYS FOR *Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.*

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	
ACTAVIS SOUTH ATLANTIC LLC,	)	
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest"), for their Complaint against defendant Actavis South Atlantic LLC ("Actavis"), allege as follows.

PARTIES

1. Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceutical company engaged in the research, development, sale and marketing of prescription pharmaceuticals used primarily to treat and manage pain, including OPANA® ER.

2. Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. Penwest is a

drug development company focused primarily on the identification, development and commercialization of products for diseases of the nervous system using its expertise in drug development and drug delivery technology, including the extended-release technology used in OPANA® ER.

3. Upon information and belief, Actavis is a limited liability company, organized and existing under the laws of the State of Delaware, having its principal place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325.

4. Upon information and belief, Actavis is in the business of manufacturing generic drug products for sale and use throughout the United States, including in this judicial district.

NATURE OF ACTION

5. This is an action for infringement of United States Patent No. 5,958,456 ("the '456 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

7. This Court has jurisdiction over Actavis, for among other reasons, Actavis has continuous and systematic contacts within this judicial district and Actavis directly, or through its divisions, subsidiaries, parent, agents and/or alter-egos maintains executive offices and a manufacturing facility in this judicial district.

FACTUAL BACKGROUND

8. On September 28, 1999, the PTO duly and legally issued the '456 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. A true and correct copy of the '456 patent is attached as Exhibit A.

9. Penwest is the assignee and owner of the '456 patent, and Endo is an exclusive licensee of this patent in the relevant field of use pursuant to a strategic alliance agreement with Penwest.

10. On June 22, 2006, the United States Food and Drug Administration (the "FDA") approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which contain oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

11. On October 19, 2007, Endo submitted information regarding the '456 patent to the FDA for listing in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book"), with respect to OPANA® ER tablets. The FDA thereafter listed the '456 patent in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

12. Upon information and belief, Actavis has submitted to the FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of oxymorphone hydrochloride extended-release tablets as generic versions of OPANA® ER tablets. Upon information and belief, this ANDA submission has been designated as ANDA No. 79-046.

13. On or about February 12, 2008, Actavis sent Penwest and Endo a notice stating that it had submitted an ANDA seeking approval to manufacture, use, or sell generic oxymorphone hydrochloride extended-release tablets in 5, 10, 20, and 40 mg strengths prior to the expiration of the '456 patent (the "First Actavis Notice").

14. The First Actavis Notice advised Penwest and Endo that Actavis's ANDA included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "paragraph IV certification") that, in Actavis's opinion, the claims of the '456 patent are invalid and/or that the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '456 patent.

15. On March 28, 2008, within 45 days of receipt of the First Actavis Notice, Endo and Penwest filed a complaint against Actavis in the District of New Jersey alleging patent infringement of the '456 patent. In their complaint, Penwest and Endo asserted that Actavis's submission of an ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constituted infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A). The civil action that was commenced by the filing of Endo's and Penwest's complaint was assigned the civil action number 08-1563 (KSH) (PS) and is currently pending in this district.

16. On or about May 29, 2008, Actavis sent Penwest and Endo a second notice stating that it had amended ANDA No. 79-046 to seek approval to manufacture, use, or sell 7.5 mg and 15 mg doses of generic oxymorphone hydrochloride extended-release tablets prior to the expiration of the '456 patent (the "Second Actavis Notice").

17. On or about June 30, 2008, Actavis sent Penwest and Endo a third notice stating that it had further amended ANDA No. 79-046 to seek approval to manufacture, use, or

sell 30 mg doses of generic oxymorphone hydrochloride extended-release tablets prior to the expiration of the '456 patent (the "Third Actavis Notice").

18. The Second and Third Actavis Notices each advised Penwest and Endo that Actavis's amended ANDA included a paragraph IV certification that, in Actavis's opinion, the claims of the '456 patent are invalid and/or that the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets in the 7.5, 15 and 30 mg strengths described in its amended ANDA would not infringe any claim of the '456 patent.

COUNT I

INFRINGEMENT OF THE '456 PATENT

19. Plaintiffs incorporate each of the preceding paragraphs 1 to 17 as if fully set forth herein.

20. Actavis's submission to the FDA of an ANDA and amendments thereto, including the § 505(j)(2)(A)(vii)(IV) allegations of which it first notified plaintiffs on February 12, 2008 and then again on May 29 and June 30, 2008, constitutes infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A).

21. Actavis's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets in the strengths set forth in its February 12, 2008, May 29, 2008 and June 30, 2008 notice letters would infringe the '456 patent.

22. Upon information and belief, Actavis was aware of the existence of the '456 patent as demonstrated by its reference to that patent in its ANDA and amendments thereto, and was aware that the filing of its Paragraph IV Certifications with respect to the '456 patent would constitute infringement of that patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Actavis has infringed the '456 patent;

B. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Actavis's ANDA No. 79-046 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), as amended, shall not be earlier than the expiration date of the '456 patent, including any extensions;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Actavis, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '456 patent for the full terms thereof, including any extensions; and

D. Costs and expenses in this action; and

E. Such other and further relief as the Court may deem just and proper.

DECHERT LLP

s/ Robert D. Rhoad

Robert D. Rhoad
Thomas P. Lihan
902 Carnegie Center, Suite 500
Princeton, NJ 08540
(609) 955-3200

Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Of Counsel:

Martin J. Black
George G. Gordon
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808
(215) 994-4000

Ann M. Caviani Pease
DECHERT LLP
2440 W. El Camino Real
Suite 700
Mountain View, CA 94040-1499
(650) 813-4800

July 11, 2008

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that as set forth in paragraph 15 of the Complaint above, the parties to this action are also the parties in a separate action filed on March 28, 2008 involving a claim for infringement of the same '456 patent that is at issue here and involving the same ANDA No. 79-046, as originally filed, at issue here. That case is encaptioned *Endo Pharmaceuticals, et al. v. Actavis South Atlantic LLC*, United States District Court, District of new Jersey, Civil Action No. 08-1563 (KSH) (PS). To the best of my knowledge, information and belief, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Date: July 11, 2008

By: s/ Robert D. Rhoad
Robert D. Rhoad

EXHIBIT A

US005958456A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,958,456

[45] Date of Patent: *Sep. 28, 1999

[54] **CONTROLLED RELEASE FORMULATION (ALBUTEROL)**

[75] Inventors: **Anand Baichwal**, Wappingers Falls, N.Y.; **Troy W. McCall**, New Milford, Conn.

[73] Assignee: **Edward Mendell Co., Inc.**, Patterson, N.Y.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/886,496**

[22] Filed: **Jul. 1, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/553,008, Nov. 3, 1995, Pat. No. 5,662,933, which is a continuation-in-part of application No. 08/118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/489**; 424/488; 424/457; 424/468

[58] **Field of Search** 424/489, 488, 424/457, 468

[56] **References Cited**

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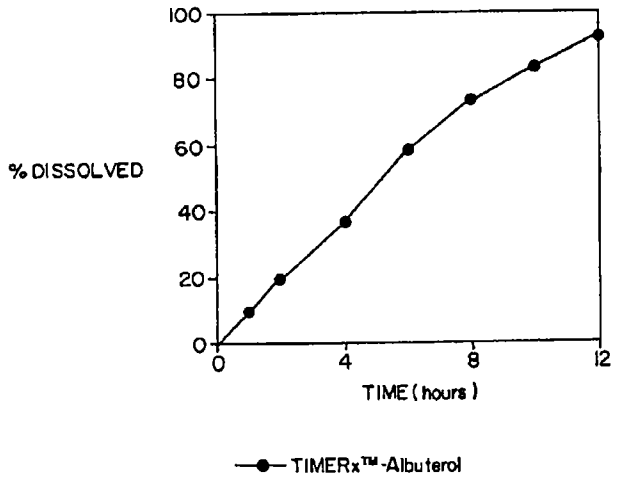
Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Davidson,Davidson & Kappel,LLC

[57] **ABSTRACT**

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

16 Claims, 3 Drawing Sheets



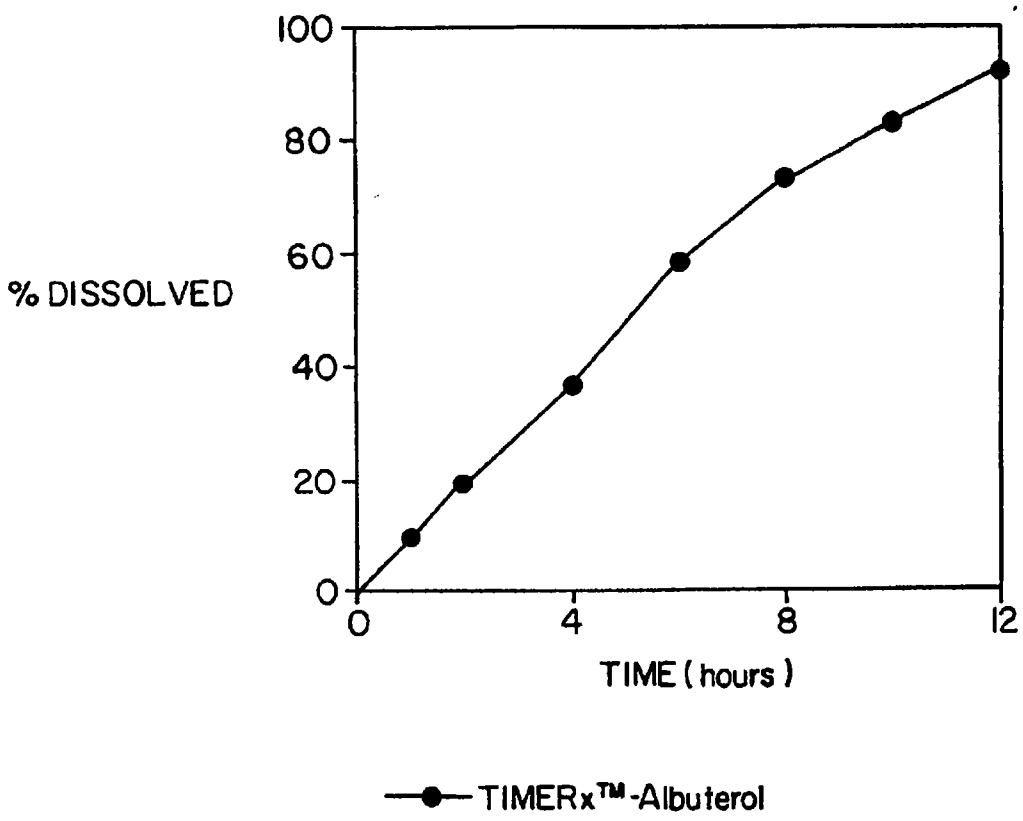

100
80
60
40
20
0
% DISSOLVED
0
4
8
12
TIME (hours)
TIMERx™-Albuterol

FIG. 1

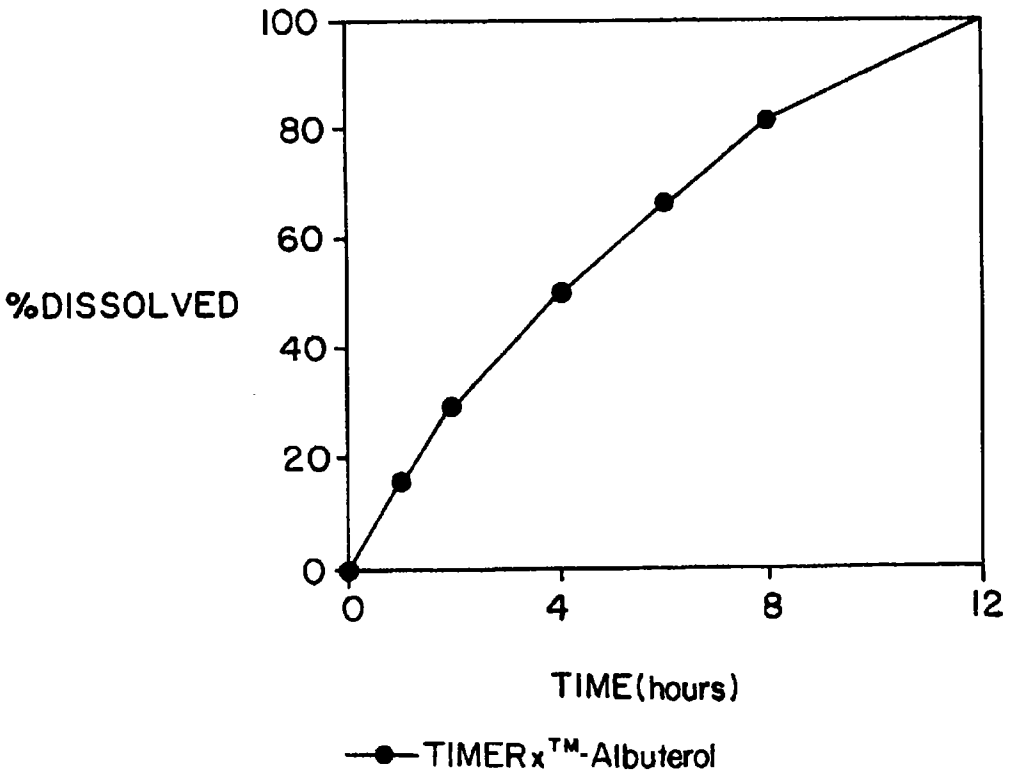

100
80
60
40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

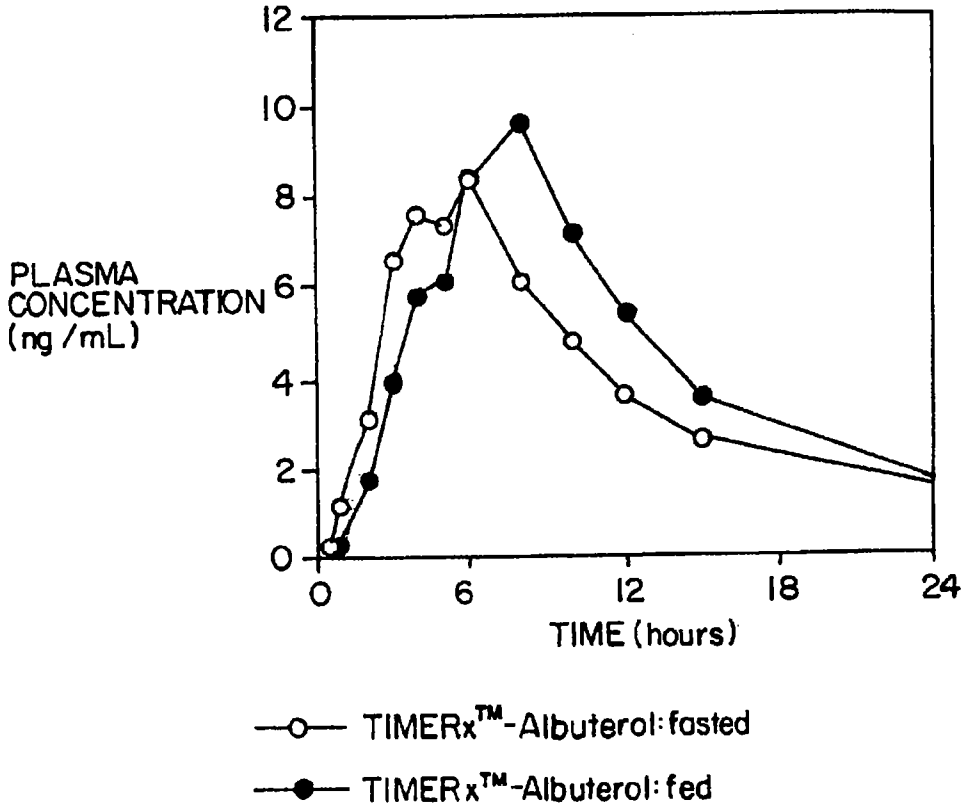

PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 08/553,008, filed Nov. 3, 1995, now U.S. Pat. No. 5,662,933, which is a continuation-in-part of Ser. No. 08/118,924, filed Sep. 9, 1993, now U.S. Pat. No. 5,455,046.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a

homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_∞"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_∞ ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_∞ (fasting patient) to AUC_∞ (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, Iowa 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g, 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), antitussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead or the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2-selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such

pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and $time_{\Delta}$ to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt (mg)	334.6	204.7
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

	Component	Example 3	Example 4
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	CAP	10	30
4.	Dextrose	60	40
5.	Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

	Component	Example 3	Examples 4
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

	Example 3	Example 4
Time (hrs)		
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

	Component	Example 5	Example 6
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	PVAP	10	30
4.	Dextrose	60	40
5.	Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

	Component	Example 5	Example 6
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

	Example 5	Example 6
Time (hrs)		
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean

gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

	Component	Example 7	Example 8
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	HPMCP	10	30
4.	Dextrose	60	40
5.	Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

	Component	Example 7	Example 8
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

	Example 7	Example 8
Time (hrs)		
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	63.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

	Component	Excipient for Examples 9–12
1.	Xanthan gum	12%
2.	Locust bean gum	18
3.	Dextrose	65
4.	EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ®, from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250, 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

	Component	Percent
1.	SRE*	8.2%
2.	Albuterol sulfate	5.3
3.	Polyvinyl acetate phthalate	5.0
4.	Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	⅜			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0–1 hr pH 1.5 1–2 hr pH 3.5 2–4 hr pH 5.5 4–12 hr pH 7.5	30% peanut oil
Agitation:	15 cpm	15 cpm
Volume:	250 mL	250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

Results and Discussion

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 though 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max}, and AUC_{28} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter	TIMERx fasted	TIMERx fed
Cmax		
mean	10.5	10.6
% CV	39.0	31.0
Tmax		
mean	4.5	7.0
% CV	29.0	23.0
AUCInf		
mean	113.4	128.1
% CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted:TIMERx fed	0.98	0.64	0.89
TIMERx fed:TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

Conclusion

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various

modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent; a pharmaceutically acceptable hydrophobic material; and an inert pharmaceutical diluent wherein the ratio of said inert diluent to said gelling agent is from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The controlled release solid dosage form according to claim **1** wherein said inert diluent is selected from the group consisting of pharmaceutically acceptable saccharides, polyhydric alcohols, pre-manufactured direct compression diluents, and mixtures of any of the foregoing.

3. The controlled release solid dosage form according to claim **1**, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

4. The controlled release solid dosage form according to claim **1**, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

5. The controlled release solid dosage form according claim **1**, wherein said hydrophobic material is present in an amount ranging from about 25 percent to about 50 percent, by weight, of the solid dosage form.

6. The controlled release solid dosage form according to claim **1**, wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

7. The controlled release solid dosage form according to claim 1 which is a tablet.

8. The controlled release solid dosage form according to claim **1**, which is in granulate form.

9. The controlled release solid dosage form according to claim **8**, wherein said granulate is coated with a hydrophobic material to a weight gain from about 1 percent to about 20 percent.

10. The controlled release solid dosage form according to claim **1**, wherein the medicament comprises an amount of albuterol equivalent to about 4 mg to about 16 mg of albuterol free base.

11. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing of a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to about 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding a therapeutically effective amount of a medicament to said excipient, such that

a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

12. The method of claim **11**, further comprising compressing said mixture of said sustained release excipient and said medicament into tablets.

13. The method of claim **11**, wherein said medicament is albuterol or a salt or derivative thereof.

14. The method of claim **13**, further comprising coating the resultant tablets with a hydrophobic coating to a weight gain from about 1 percent to about 20 percent.

15. A method of treating a patient with albuterol comprising:

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of albuterol or a salt or derivative thereof to said sustained release excipient, tableting the resultant mixture into tablets such that said tablets have a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol for at least 12 hours; and

administering said tablet to a patient on a once-a-day or twice-a-day basis.

16. The method of claim **15**, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,958,456
APPLICATION NO. : 08/886496
DATED : September 28, 1999
INVENTOR(S) : Baichwal et al.

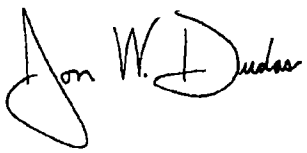
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the bibliographic of the patent in line 2 of the text at bracket 63, between "continuation in part of" and "application" insert --application No. 08/447,236, May 22, 1995, U.S. Pat. No. 5,554,387, which is a divisional of--.

In the patent at Col. 1, line 9, between "continuation-in-part of" and "Ser. No." insert --Ser. No. 08/447,236, filed May 22, 1995, now U.S. Pat. No. 5,554,387, which is a divisional of--.

Signed and Sealed this

Fifth Day of February, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT E

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
SAIBER LLC
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Tel: (903) 622-3333
Fax: (903) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
VINSON & ELKINS LLP
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Tel : (512) 542-8504
Fax : (512) 236-3278

Attorneys for Defendant and Counterclaim Plaintiff
Actavis South Atlantic LLC

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC. and PENWEST PHARMACEUTICALS CO.,	)	CIVIL ACTION NO. 08-3482 (KSH) (PS)
Plaintiffs	)	
v.	)	***Document Electronically Filed***
ACTAVIS SOUTH ATLANTIC LLC	)	
Defendant.	)	

DEFENDANT ACTAVIS SOUTH ATLANTIC LLC'S ANSWER, SEPARATE DEFENSES, COUNTERCLAIMS AND DEMAND FOR JURY TRIAL

Defendant Actavis South Atlantic LLC ("ASA"), by its attorneys, responds to the averments made in the numbered paragraphs of the Complaint filed by Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest") as follows:

1. On information and belief, ASA admits that Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317, and that Endo sells OPANA® ER. ASA is without specific knowledge or information sufficient to form a belief as to the remaining allegations in this paragraph and, on that basis, denies them.

2. On information and belief, ASA admits that Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. ASA is without specific knowledge or information sufficient to form a belief as to the remaining allegations in this paragraph and, on that basis, denies them.

3. ASA admits the allegations in paragraph 3.

4. ASA admits that it manufactures generic drug products for sale and use in the United States and in this district, but denies the remaining allegations in paragraph 4.

5. ASA admits that Plaintiff purports to assert an action for infringement of U.S. Patent No. 5,958,456 ("the '456 patent") and that Plaintiff's claim for patent infringement purports to arise under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, but denies the remaining allegations in paragraph 5.

6. ASA admits the allegations in paragraph 6.

7. ASA admits that jurisdiction in this district is proper, but denies the remaining allegations in paragraph 7.

8. ASA admits that the '456 patent, entitled "Controlled Release Formulation (Albuterol)", purports on its face to have been issued by the United States Patent and Trademark Office ("USPTO") on September 28, 1999 to Edward Mendell Co., Inc. as the

named assignee and admits that a copy of the '456 patent was attached as Exhibit A as alleged in paragraph 8, but denies the remaining allegations in paragraph 8.

9. ASA is without specific knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 9 and, on that basis, denies them.

10. On information and belief, ASA admits that New Drug Application ("NDA") No. 21-610 for OPANA® ER tablets was approved on June 22, 2006, as alleged in paragraph 10, but avers that the NDA speaks for itself with respect to its contents. ASA denies the remaining allegations in paragraph 10.

11. ASA admits that the Food and Drug Administration ("FDA") has listed the '456 patent in its publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") as alleged in paragraph 11, but ASA is without specific knowledge or information sufficient to form a belief as to the truth of the remaining allegations in paragraph 11 and, on that basis, denies them.

12. ASA admits that it filed Abbreviated New Drug Application ("ANDA") No. 79-046 with the FDA under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacturing, use or sale of oxymorphone hydrochloride extended release tablets as alleged in paragraph 12, but denies the remaining allegations in paragraph 12.

13. ASA admits the allegations in paragraph 13.

14. ASA admits the allegations in paragraph 14.

15. ASA admits the allegations in paragraph 15.

16. ASA admits the allegations in paragraph 16.

17. ASA admits the allegations in paragraph 17.

18. ASA admits the allegations in paragraph 18.

RESPONSE TO COUNT I

(Alleged Infringement of the '456 Patent)

19. ASA reasserts and incorporates by reference each of the answers to paragraphs 1-18 above, as if fully set forth herein.

20. ASA denies the allegations in paragraph 20.

21. ASA denies the allegations in paragraph 21.

22. ASA admits that the Paragraph IV certification in its ANDA references the '456 patent as alleged in paragraph 22, but denies the remaining allegations in paragraph 22.

SEPARATE DEFENSES

Without any admission as to the burden of proof or as to any of the averments in the Complaint, ASA sets forth the following defenses:

FIRST SEPARATE DEFENSE

23. ASA has not infringed any claim of the '456 patent, either literally or under the doctrine of equivalents.

SECOND SEPARATE DEFENSE

24. ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 will not infringe any claim of the '456 patent, either literally or under the doctrine of equivalents.

THIRD SEPARATE DEFENSE

25. Plaintiff is barred by 35 U.S.C. § 288 from recovering any costs associated with this suit.

FOURTH SEPARATE DEFENSE

26. The claims of the '456 patent are invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

FIFTH SEPARATE DEFENSE

27. The claims of the '456 patent are invalid under the judicially created doctrine of non-statutory, obviousness-type double patenting.

SIXTH SEPARATE DEFENSE

28. The doctrine of prosecution history estoppel precludes a finding that ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 would infringe the claims of the '456 patent by equivalence.

SEVENTH SEPARATE DEFENSE

29. The claims of the '456 patent will not be not infringed by ASA's commercial manufacture, use, offer for sale or sale of its proposed oxymorphone hydrochloride extended release tablets identified in ANDA No. 79-046 under the doctrine of equivalents because all embodiments described in prior patents in the '456 patent family and/or in the '456 patent but not claimed by them are dedicated to the public.

EIGHTH SEPARATE DEFENSE

30. The claims of the '456 patent are unenforceable due to inequitable conduct committed during prosecution of the '456 patent and/or prior patents in the same patent family.

31. On its face, the '456 patent was filed as U.S. Pat. App. No. 08/866,496 ("the '496 application") and purports to be a continuation of U.S. Pat. App. No. 08/553,008 ("the '008 application"), issued as U.S. Pat. No. 5,662,933 ("the '933 patent").

32. The '933 patent, in turn, purports to be a continuation-in-part of U.S. Pat. App. No. 08/118,924 ("the '924 application"), issued as U.S. Pat. No. 5,455,046 ("the '046 patent").

33. On information and belief, the '924, '008 and '496 applications were assigned to Edward Mendell Co., Inc. ("Mendell") during their prosecution. On information and belief, Mendell was renamed Penwest Pharmaceuticals Co. on October 20, 1997.

34. The same attorney prosecuted the '924, '008 and '496 applications.

35. On information and belief, the issue notification for the '924 application was mailed on August 28, 1995 to the attorney prosecuting the '924 application. The '924 application — the purported grandparent application of the '456 patent — issued as the '046 patent on October 3, 1995.

36. The '008 application — the purported parent application of the '456 patent — was filed on November 3, 1995, one month after the '046 patent issued, by the same attorney that paid the issue fee in the '924 application.

37. Despite a lack of co-pendency between the '924 and '008 applications, Mendell nevertheless included the following reference to the '924 application in the '008 specification when the '008 application was filed: "The present application is a continuation-in-part of U.S. application serial number 08/118,924, filed on September 9, 1993[.]" The issuance of and the patent number for the '046 patent were not included in the specification upon filing.

38. As part of the initial filing of the '008 application on November 3, 1995, Mendell filed an unsigned declaration with the '008 application. That declaration contained a

claim of priority to Application Serial No. 07/781,980, an unrelated application, and did not contain a priority claim to the '924 application, which had issued as the '046 patent as of the filing date of the '008 application.

39. Mendell subsequently filed a signed declaration for the '008 application on January 16, 1996. This declaration did not contain a claim of priority. The priority claim to Application Serial No. 07/781,980 (the unrelated application) was deleted in this declaration.

40. The issue fee in the '008 application was paid on March 26, 1997.

41. On June 17, 1997, after payment of the issue fee and, on information and belief, without any additional correspondence from the USPTO, Mendell filed a third "Supplemental Declaration."

42. This Supplemental Declaration included a claim of priority to the '924 application and noted that the '924 application was "[p]atented as U.S. 5,455,046." This Supplemental Declaration was filed by the same attorney that paid the issue fee in the '924 application and filed the '008 application. The substantive content of the Supplemental Declaration did not differ in any way from the declaration filed on January 16, 1996, except that the priority claim to the '924 application was added.

43. Despite its awareness of the issuance of the '046 patent as evidenced by the inclusion of the patent number in the Supplemental Declaration, Mendell did not inform the USPTO of the lack of co-pendency prior to the issuance of the '933 patent.

44. Additionally, Mendell never informed the USPTO of the lack of co-pendency during the prosecution of the application that became the '456 patent, even though it also contains an alleged claim of priority to the '046 patent.

45. In sum, despite a lack of co-pendency as required under 35 U.S.C. § 120, Mendell intentionally misrepresented to the USPTO its entitlement to the benefit of the earlier filing date of the '924 application when it filed the '008 application (which issued as the '933 patent and is the purported parent of the '456 patent asserted in this case) with a priority claim to the '924 application.

46. Mendell again intentionally misrepresented its entitlement to the filing date of the '924 application when it filed the application issuing as the '456 patent.

47. Entitlement to an earlier priority date is inherently material to patentability as a matter of law.

48. In light of the intentional misrepresentations of entitlement to priority during the prosecution of the applications that issued as the '933 and '456 patents, the '456 patent is unenforceable due to inequitable conduct.

NINTH SEPARATE DEFENSE

49. ASA repeats and incorporates by reference paragraphs 30 through 48 herein.

50. In addition to misrepresenting its entitlement to an earlier priority date, Mendell also intentionally failed to disclose to the USPTO numerous references that are highly material to the patentability of the claims of the '933 and '456 patents.

51. The '496 application, which issued as the '456 patent, was filed in the names of Anand Baichwal ("Baichwal") and Troy W. McCall ("McCall"). Baichwal and McCall assigned the '496 application to Mendell, which was later renamed Penwest. On information and belief, Baichwal is currently the Senior Vice President of Licensing and Chief Scientific Officer of Penwest.

52. Baichwal is a named inventor on, and Penwest is the assignee of, at least seven patents covering subject matter similar to the subject matter of the claims of the '046, '933 and '456 patents that were not disclosed to the USPTO during prosecution. The non-disclosed Baichwal patents assigned to Penwest include at least: U.S. Pat. Nos. 5,169,639; 5,330,761; 5,399,358; 5,399,359; 5,399,362; 5,472,711; and 5,478,574.

53. The assistant patent examiners indicated on the face of these seven patents are different than the assistant examiners indicated on the face of the '046, '933 and '456 patents.

54. These seven patents are highly material to the patentability of the claims of the '933 and '456 patents.

55. For example, in one instance during prosecution of the application which became the '046 patent, the USPTO rejected the pending, non-withdrawn claims over two patents related to one of the non-disclosed patents, namely U.S. Pat. No. 5,169,639 ("the '639 patent").

56. The '639 patent is a continuation-in-part of U.S. Pat. No. 5,128,143 ("the '143 patent"), which is a continuation-in-part of U.S. Pat. No. 4,994,276 ("the '276 patent"). On information and belief, the '639 patent was prosecuted by the same attorney that prosecuted the '924 application. The '639 patent issued before the '924 application was filed.

57. During prosecution of the '924 application, the USPTO rejected all of the pending, non-withdrawn claims of the '924 application for statutory and non-statutory, obviousness-type double patenting over claims 1-24 of the '143 patent, the parent of the '639 patent.

58. In that same office action, the USPTO rejected all of the pending, non-withdrawn claims of the '924 application for statutory and non-statutory, obviousness-type

double patenting over claims 1-18 of U.S. Patent No. 4,994,276 (the grandparent of the '639 patent), which lists Baichwal as an inventor and which was assigned to Penwest.

59. Despite receiving these statutory and non-statutory, obviousness-type double patenting rejections over the '143 and '276 patents, Baichwal and Mendell did not disclose the existence of the '639 patent (the child and grandchild of the '143 and '276 patents) to the USPTO during prosecution of the '924, '008, or '496 applications.

60. In sum, after receiving double patenting rejections over Baichwal patents related to the subject matter of the '924, '496 or '008 applications, Baichwal and Mendell (now Penwest) never disclosed to the USPTO the existence of at least seven other Baichwal patents related to similar subject matter.

61. Additionally, at least two of the non-disclosed Baichwal patents anticipate one or more claims of the '933 and '456 patents, and thus, these patents are highly material to patentability.

62. For example, the '639 patent and U.S. Pat. No. 5,330,761, another one of the at least seven, non-disclosed Baichwal patents, are prior art to the '933 and '456 patents under section 102(b), and both of the patents anticipate one or more of the claims of the '933 and '456 patents because the '933 and '456 patents are not entitled to claim priority to the '046 patent. Thus, these patents are highly material to patentability.

63. In addition to failing to disclose the Baichwal patents, Baichwal and Mendell also failed to disclose the formulation and ingredients of Calan® SR to the USPTO during prosecution of the '924, '008 and '496 applications.

64. Baichwal and Mendell were in possession of Calan® SR on or before March 9, 1990 and had conducted comparative experiments between Calan® SR and their own slow release excipients on or before that date.

65. Baichwal and Mendell knew the formulation and ingredients of Calan® SR during prosecution of the '924, '008 and '496 applications.

66. Calan® SR anticipates one or more claims of the '456 patent, and as such, is highly material to the patentability.

67. In light of the foregoing, the claims of the '456 patent are unenforceable because of inequitable conduct committed during the prosecution of the '924 and '008 applications and again during prosecution of the application issuing as the '456 patent.

TENTH SEPARATE DEFENSE

68. ASA repeats and incorporates by reference paragraphs 30 through 67 herein.

69. In addition to misrepresenting its entitlement to an earlier priority date and intentionally failing to disclose to the USPTO numerous highly material references, Penwest also intentionally misrepresented its right to Certificates of Correction for the '933 and '456 patents to the USPTO.

70. In an attempt to repair the priority defect in the '933 and '456 patents, set out above in paragraphs 30-48, Penwest requested Certificates of Correction under 35 U.S.C. § 255 for the '933 and '456 patents on or about December 28, 2007, more than eight years after the '456 patent issued and more than eleven years after the '933 patent issued.

71. Penwest's Certificates of Correction insert, for the first time, a priority claim to U.S. Pat. App. No. 08/447,236 ("the '236 application").

72. There was no mention or reference to the '236 application in the prosecution history of the '933 or '456 patents prior to December 28, 2007, and moreover, the '933 and '456 patents contain substantially different subject matter than that disclosed in the '236 application.

73. Consequently, Plaintiffs' amendments to claim priority to the '236 application amount to little more than plucking any copending, but otherwise distantly related, application which was previously outside the chain of priority from the Applicants' patent portfolio to resuscitate the '933 and '456 patents' claims to an earlier priority date.

74. Such amendments are not proper under the USPTO's requirements for post-issuance correction of priority claims.

75. Plaintiffs intentionally misrepresented their right to these Certificates of Correction.

76. The proper route for any correction would have been for Penwest to seek a reissue patent, but Penwest chose not to file for reissue knowing that this would give rise to intervening rights for ASA.

77. In light of the foregoing, the claims of the '456 patent are unenforceable because of inequitable conduct committed during the prosecution of the '924 and '008 applications, again during prosecution of the application issuing as the '456 patent, and again in seeking Certificates of Correction for the '933 and '456 patents.

ELEVENTH SEPARATE DEFENSE

78. Plaintiffs apparently assert the '456 patent, inclusive of a Certificate of Correction issued on February 5, 2008, against ASA.

79. On information and belief, Plaintiffs requested the Certificate of Correction for the '456 patent under 35 U.S.C. § 255, which is entitled "Certificate of Correction of Applicant's Mistake," on or about December 28, 2007.

80. In requesting the Certificate of Correction, Plaintiffs sought to repair—some eight years after issuance—the priority defects of the '456 patent by inserting a reference to the '236 application, even though that application was never referenced in prosecution prior to issuance.

81. As set out in detail above in paragraphs 30-48, during the pendency of the application that issued as the '456 patent, Mendell failed in three separate attempts to properly claim priority to any copending application, thereby misrepresenting its entitlement to an earlier priority date. Even despite knowing that the priority of the '456 application was improper on January 19, 1996 and June 24, 1997, Mendell failed at those times to refer to the '236 application.

82. Despite failing to claim priority to the '236 application on 3 separate occasions, including two times while the applicant was correcting priority, Plaintiffs claim to have discovered in 2007, over eight years after the issuance of the '456 patent, that the priority claim to the '236 application was clear from the record and its omission was a mistake made in good faith.

83. No evidence supports that the appropriateness of the correction was clear from the record. On information and belief, the applicant of the '456 application intentionally did not claim priority to the '236 application.

84. Because such a correction does not comply with the requirements of 35 U.S.C. § 255, the Certificate of Correction for the '456 patent is invalid.

85. Consequently, the '456 patent cannot claim priority to a date any earlier than November 3, 1995, the purported filing date of the '933 patent, and is thus invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*

TWELFTH SEPARATE DEFENSE

86. As described in paragraphs 78-85, the Certificate of Correction for the '456 is invalid. Further, the Certificate of Correction does not apply to this action.

87. ASA filed ANDA No. 79-046 on June 8, 2007. This is the act which Plaintiffs accuse as infringing. Plaintiffs' Complaint for Patent Infringement, Paragraph 16.

88. The Certificate of Correction for the '456 patent issued on February 5, 2008, nearly 8 months after the accused act of infringement.

89. Indeed, Plaintiffs did not even request the Certificate of Correction until December 28, 2007, some six months after the accused act of infringement.

90. The FDA accepted ASA's ANDA for filing prior to December 28, 2007.

91. Because Plaintiffs' cause of action arose before the Certificate of Correction issued, the Certificate of Correction is not effective against ASA in connection with Plaintiffs' infringement claim, according to the plain language of 35 U.S.C. § 255.

92. Thus, for this cause of action, the '456 patent cannot claim priority to a date earlier than November 3, 1995, the purported filing date of the '933 patent, and is thus invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*

THIRTEENTH SEPARATE DEFENSE

93. Plaintiffs' claims are barred by the equitable doctrine of unclean hands.

FOURTEENTH SEPARATE DEFENSE

94. Plaintiffs' claims are barred by the doctrines of patent exhaustion and implied license.

COUNTERCLAIMS

ASA, by way of Counterclaim against Plaintiffs, Endo and Penwest, alleges as follows:

1. This is an action for a declaratory judgment of non-infringement, invalidity, and/or unenforceability of the one or more claims of United States Patent Nos. 5,128,143, 5,662,933, 5,958,456, and 7,276,250 ("the '250 patent), under 35 U.S.C. § 271(e)(5), 28 U.S.C. §§ 2201(a) and (b), and 21 U.S.C. § 355(j); and for unfair competition under the common law of the State of New Jersey.

The Parties

2. ASA is a limited liability corporation organized under the laws of the State of Delaware, having a principal place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325.

3. On information and belief, Counterclaim Defendant Penwest is a corporation organized under the laws of the State of Washington, having a principal place of business at 39 Old Ridgebury Road, Suite #11, Danbury, Connecticut 06810.

4. On information and belief, Counterclaim Defendant Endo is a corporation organized under the laws of the State of Delaware, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317.

Jurisdiction

5. This court has subject matter jurisdiction over these Counterclaims for declaratory judgment pursuant to 35 U.S.C. § 271(e)(5); 28 U.S.C. §§ 1331, 1337(a), 1338(a) and (b),

2201(a) and (b); and 21 U.S.C. § 355(j), based on an actual controversy between ASA and counterclaim-defendants arising under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* This court has supplemental jurisdiction over ASA's state law claims pursuant to 28 U.S.C. § 1367.

6. This court has personal jurisdiction over Endo and Penwest based, *inter alia*, on the filing by Endo and Penwest of this lawsuit in this jurisdiction.

7. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c).

Orange Book Listing of the '143, '933, '456, and '250 Patents

8. On information and belief, Penwest is the assignee of the '143, '933, '456, and '250 patents.

9. On information and belief, Penwest has exclusively licensed the '143, '933, '456, and '250 patents to Endo for the manufacture and sale of Endo's oxymorphone hydrochloride extended release drug product, marketed under the name OPANA® ER.

10. On information and belief, pursuant to 21 U.S.C. § 355(b)(1)(G), Endo and/or Penwest caused the FDA to publish the '143, '933, '456 and '250 patents in the Orange Book in connection with NDA No. 02-1610 for OPANA® ER ("the OPANA® ER NDA").

11. Endo and/or Penwest submitted information regarding the '933 and '456 patents to the FDA for publication in the Orange Book in violation of the time requirements for the submission of patent information set forth in 21 C.F.R. § 314.53.

12. Endo and/or Penwest late listed the '933 and '456 patents in the Orange Book after becoming aware of the filing of an ANDA for oxymorphone hydrochloride extended release tablets by Impax Laboratories, Inc. with the intent of delaying the approval of any and all ANDAs for oxymorphone hydrochloride extended release tablets.

13. Endo and/or Penwest late listed the '933 and '456 patents in the Orange Book because they knew that the '143 and '250 patents could not be asserted against Impax, and thus, the listing of the '933 and '456 patents in the Orange Book was designed to manufacture a 30-month stay of approval of Impax's ANDA and delay approval of any subsequent ANDAs.

14. By maintaining the listing of these patents in the Orange Book, Endo represents that the '143, '933, '456, and '250 patents "could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1)(G).

ASA's Abbreviated New Drug Application

15. On June 8, 2007, ASA filed ANDA No. 79-046 ("the ASA ANDA") with the FDA seeking approval to market its proposed oxymorphone hydrochloride extended release tablets in 20 mg and 40 mg strengths. On June 13, 2007, ASA filed an amendment to the ASA ANDA seeking approval to market and sell 5 and 10 mg strength oxymorphone hydrochloride extended release tablets (all strengths collectively referred to as "ASA's oxymorphone products").

16. The FDA thereafter accepted the ASA ANDA for filing.

17. As part of its ANDA filing, ASA certified to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification"), that the manufacture, use and/or sale of ASA's oxymorphone products will not infringe the claims of the '143, '933, '456 and '250 patents and/or that the claims of those patents are invalid.

18. On February 12, 2008, in accordance with the requirements of 21 U.S.C. § 355(j)(2)(B), ASA mailed Penwest and Endo notice letters that it had filed the ASA ANDA containing a Paragraph IV certification regarding the '143, '933, '456 and '250 patents.

19. On May 29, 2008, ASA filed an amendment the ASA ANDA seeking approval to market and sell 7.5 and 15 mg strength oxymorphone hydrochloride extended release tablets.

20. On June 30, 2008, ASA filed an amendment to the ASA ANDA seeking approval to market and sell 30 mg strength oxymorphone hydrochloride extended release tablets.

21. On May 29, 2008 and June 30, 2008, respectively, in accordance with 21 U.S.C. § 355(j)(2)(B)(ii)(II), ASA mailed Penwest and Endo notice letters that it had filed amendments to the ASA ANDA for the 7.5, 15, and 30 mg strength oxymorphone hydrochloride extended release tablets.

22. ASA's notice letters provided a detailed statement of the factual and legal basis establishing that the claims of the '143, '933, '456 and '250 patents are invalid and/or will not be infringed by the manufacture, use or sale of ASA's oxymorphone products.

23. As part of ASA's notice letters to Penwest and Endo, and in accordance with the requirements of 21 U.S.C. § 355(j)(5)(C)(i), ASA offered Penwest and Endo confidential access to the ASA ANDA.

24. Penwest and Endo received the notice letters no later than February 15, 2008.

The Presence of a Case or Controversy

25. By maintaining the Orange Book listing of the '143, '933, '456 and '250 patents in connection with the OPANA® ER NDA, Penwest and its exclusive licensee, Endo, continue to represent that the '143, '933, '456 and '250 patents could reasonably be asserted against anyone making, using or selling a generic extended release oxymorphone hydrochloride product without a license from Penwest.

26. Penwest and Endo have issued joint press releases stating their intent "to pursue all available legal and regulatory avenues in defense of OPANA ER, including enforcement of their intellectual property rights and approved labeling."

27. ASA's Paragraph IV certification states that ASA's oxymorphone products do not infringe any claim of the '143, '933, '456 and '250 patents and/or that the claims of those patents are invalid.

28. In response to ASA's ANDA filing and Paragraph IV certification against all four Orange Book listed patents, Penwest and Endo filed an infringement action under 35 U.S.C. § 271(e)(2)(A) selectively asserting only the '456 patent, thus gaining the exclusionary benefit of an automatic 30-month stay of approval of ASA's ANDA while jeopardizing only the '456 patent in litigation.

29. The statutory 45-day period following Endo and Penwest's receipt of the notice letter expired on March 31, 2008, and neither Endo nor Penwest has asserted the '143, '933, or the '250 patents against ASA.

30. 35 U.S.C. § 271(e)(5) provides that the Court shall have subject matter jurisdiction under 28 U.S.C. § 2201 for a declaratory judgment claim that an Orange Book listed patent that is not asserted during the statutory 45-day period is invalid and/or not infringed.

31. On information and belief, Penwest has asserted the '933 and '456 patents in a similar infringement action against another ANDA filer, Impax Laboratories, Inc., in connection with Impax's ANDA seeking approval to market an extended release oxymorphone hydrochloride product, styled *Endo Pharmaceuticals Inc. v. Impax Laboratories, Inc.*, C.A. No. 08-057, D. Del.

32. Should ASA prevail in this litigation with Penwest and Endo asserting only the '456 patent, ASA would still be faced with the threat of litigation from Penwest and Endo over the three remaining Orange Book listed patents, all relating to the same controversy of the instant '456 action — ASA's ANDA filing and the ASA oxymorphone products.

33. Additionally, if ASA succeeds in proving that ASA has not infringed and that ASA's oxymorphone products will not infringe the '143, '933, '456 or '250 patents and/or that those patents are invalid, such a judgment will remove any independent barriers to competition that may exist by virtue of Penwest and/or Endo's maintenance of the listing of these patents in the Orange Book in connection with the OPANA® ER NDA.

34. In light of all the circumstances, an actual substantial and continuing justiciable controversy having sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Penwest and ASA as to whether the claims of the '143, '933, '456 and '250 patents are invalid and/or not infringed by ASA.

FIRST COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,128,143)

35. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

36. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 1 of the '143 patent.

37. ASA's oxymorphone products do not contain "xanthan gum and a galactomannan gum capable of cross-linking said xanthan gum in the presence of aqueous solutions" or any equivalent thereto.

38. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 1 of the '143 patent.

39. Further, ASA's oxymorphone products will not infringe at least claim 1 of the '143 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone products infringe by equivalence.

40. Thus, ASA is entitled to a declaratory judgment that ASA has not infringed and ASA's oxymorphone products will not infringe at least claim 1 of the '143 patent.

SECOND COUNT
(Declaratory Judgment of Invalidity, United States Patent No. 5,662,933)

41. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

42. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the invalidity of at least claim 6 of the '933 patent.

43. At least claim 6 of the '933 patent is invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

44. At least claim 1 of the '933 patent is invalid under the judicially created doctrine of non-statutory, obviousness-type double patenting.

45. Thus, ASA is entitled to a declaratory judgment that at least claims 1 and 6 of the '933 patent are invalid.

THIRD COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,662,933)

46. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

47. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 9 of the '933 patent.

48. ASA's oxymorphone products do not contain "albuterol or a salt or derivative thereof" or any equivalent thereto.

49. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 9 of the '933 patent.

50. Further, ASA's oxymorphone products will not infringe at least claim 9 of the '933 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone products infringe by equivalence.

51. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone products will not infringe at least claim 9 of the '933 patent.

FOURTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,662,933)

52. ASA repeats and incorporates by reference paragraphs 30 through 48 of ASA's Answer and Separate Defenses to the Complaint.

53. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a

declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '933 patent.

54. Penwest procured the '933 patent through inequitable conduct by intentionally misrepresenting entitlement to priority, which is inherently material to patentability, to the '046 patent.

55. Thus, ASA is entitled to a declaratory judgment that the '933 patent is unenforceable due to inequitable conduct committed during the prosecution of the '933 patent.

FIFTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,662,933)

56. ASA repeats and incorporates by reference paragraphs 49 through 67 of ASA's Answer and Separate Defenses to the Complaint.

57. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '933 patent.

58. Penwest procured the '933 patent through inequitable conduct by intentionally withholding material prior art from the PTO during the prosecution of the '046, the '933 and the '456 patents.

59. Thus, ASA is entitled to a declaratory judgment that the '933 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent and/or the '046 and '933 patents.

SIXTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,662,933)

60. ASA repeats and incorporates by reference paragraphs 68 through 77 of ASA's Answer and Separate Defenses to the Complaint.

61. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '933 patent.

62. In order to correct a priority defect in the '933 patent, Penwest intentionally misrepresented its entitlement to a Certificate of Correction to the USPTO, thereby committing inequitable conduct.

63. Thus, ASA is entitled to a declaratory judgment that the '933 patent is unenforceable due to inequitable conduct committed in requesting a Certificate of Correction for the '933 patent.

SEVENTH COUNT
(Declaratory Judgment of Invalidity, United States Patent No. 5,958,456)

64. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

65. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the invalidity of the claims of the '456 patent.

66. The claims of the '456 patent are invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq*., including, without limitation, 35 U.S.C. §§ 101, 102, 103 and 112.

67. The claims of the '456 patent are invalid under the judicially created doctrine of non-statutory, obviousness-type double patenting.

68. Thus, ASA is entitled to a declaratory judgment that the claims of the '456 patent are invalid.

EIGHTH COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 5,958,456)

69. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

70. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of the claims of the '456 patent.

71. ASA has not infringed and ASA's oxymorphone products will not literally infringe any claim of the '456 patent.

72. Further, ASA's oxymorphone products will not infringe any claim of the '456 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone products infringes by equivalence.

73. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone products will not infringe any claim of the '456 patent.

NINTH COUNT

(Declaratory Judgment of Unenforceability, United States Patent No. 5,958,456)

74. ASA repeats and incorporates by reference paragraphs 30 through 48 of ASA's Answer and Separate Defenses to the Complaint.

75. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '456 patent.

76. Penwest procured the '456 patent through inequitable conduct by intentionally misrepresenting entitlement to priority, which is inherently material to patentability, to the '046 patent.

77. Thus, ASA is entitled to a declaratory judgment that the '456 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent.

TENTH COUNT

(Declaratory Judgment of Unenforceability, United States Patent No. 5,958,456)

78. ASA repeats and incorporates by reference paragraphs 49 through 67 of ASA's Answer and Separate Defenses to the Complaint.

79. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '456 patent.

80. Penwest procured the '456 patent through inequitable conduct by intentionally withholding material prior art from the PTO during the prosecution of the '046, '933 and '456 patents.

81. Thus, ASA is entitled to a declaratory judgment that the '456 patent is unenforceable due to inequitable conduct committed during the prosecution of the '456 patent and/or the '046 and '933 patents.

ELEVENTH COUNT
(Declaratory Judgment of Unenforceability, United States Patent No. 5,958,456)

82. ASA repeats and incorporates by reference paragraphs 68 through 77 of ASA's Answer and Separate Defenses to the Complaint.

83. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaration of rights by this Court exists between ASA and Penwest and Endo concerning the unenforceability of the '456 patent.

84. In order to correct a priority defect in the '456 patent, Penwest intentionally misrepresented its entitlement to a Certificate of Correction to the USPTO, thereby committing inequitable conduct.

85. Thus, ASA is entitled to a declaratory judgment that the '456 patent is unenforceable due to inequitable conduct committed while requesting a Certificate of Correction for the '456 patent.

TWELFTH COUNT
(Declaratory Judgment of Non-Infringement, United States Patent No. 7,276,250)

86. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses to the Complaint and of these Counterclaims.

87. A case of actual, substantial and continuing justiciable controversy having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a

declaration of rights by this Court exists between ASA and Penwest and Endo concerning the non-infringement of at least claim 1 of the '250 patent.

88. ASA's oxymorphone products do not contain "about 8.3% to about 41.7% by weight locust bean gum" or an equivalent thereto.

89. ASA's oxymorphone products do not contain "about 8.3% to about 41.7% by weight xanthan gum" or an equivalent thereto.

90. ASA has not infringed and ASA's oxymorphone products will not literally infringe at least claim 1 of the '250 patent.

91. Further, ASA's oxymorphone product will not infringe any claim of the '250 patent under the doctrine of equivalents, because, *inter alia*, the doctrine of prosecution history estoppel precludes a finding that ASA's oxymorphone product infringe by equivalence.

92. Thus, ASA is entitled to a declaratory judgment that ASA's oxymorphone product will not infringe at least claim 1 of the '250 patent.

THIRTEENTH COUNT
(Unfair Competition under New Jersey Common Law)

93. ASA repeats and incorporates by reference each of the foregoing paragraphs of ASA's Answer and Separate Defenses herein and of its foregoing Counterclaims herein.

94. On information and belief, Penwest has exclusively licensed the '143, '933, '456, and '250 patents to Endo for the manufacture and sale of OPANA® ER.

95. On information and belief, Penwest and Endo have joined together in the manufacture and sale of OPANA® ER and the enforcement of the '933 and '456 patents.

96. Penwest and Endo have issued joint press releases stating their intent "to pursue all available legal and regulatory avenues in defense of OPANA ER, including enforcement of their intellectual property rights and approved labeling."

97. OPANA® ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

98. The active pharmaceutical ingredient in OPANA® ER is oxymorphone hydrochloride.

99. Prescriptions written for oxymorphone hydrochloride extended release tablets can be filled only with oxymorphone hydrochloride extended release tablets.

100. At all relevant times, Penwest and Endo have sold substantial amounts of their oxymorphone hydrochloride extended release tablets throughout the United States and particularly in New Jersey.

101. Upon final approval from the FDA, ASA's oxymorphone hydrochloride extended release tablets will be substitutable for, and in direct competition with, Endo's OPANA® ER.

102. Upon final approval from the FDA, ASA plans to sell its oxymorphone hydrochloride extended release tablets throughout the United States and particularly in New Jersey.

103. However, Penwest and Endo are currently the only permitted suppliers of oxymorphone hydrochloride extended release tablets.

104. As set forth with particularity in paragraphs 30 through 77 of ASA's Answer and Separate Defenses to the Complaint herein and as further alleged herein, Penwest and Endo have engaged in unlawful acts, practices and/or policies that constitute unfair competition and/or unfair methods of competition, in violation of the common law of the state of New Jersey. Such acts, practices and/or policies, which are unfair, immoral, unconscionable, and contrary to fair play and respectable business practices, include:

A. Knowingly and fraudulently procuring the '933 and '456 patents;

B. Fraudulently listing the '933 and '456 patents in the Orange Book knowing the claims of said patents to be invalid and unenforceable;

C. Late listing the '933 and '456 patents in the Orange Book in connection with the OPANA® ER NDA in violation of 21 C.F.R. § 314.53 with the intention of delaying the approval of ANDA applications, including ASA's ANDA No. 79-046;

D. Knowingly and willfully misrepresenting their entitlement to the filing date of an earlier application and failing to disclose highly material references to the PTO examiner, in turn causing the PTO to issue the '933 and '456 patents in reliance on their fraudulent conduct; and

E. Knowingly and willfully misrepresenting to the USPTO their entitlement to Certificates of Correction for the '933 and '456 patents to correct an otherwise improper claim for priority.

105. Penwest and Endo's commercially unfair and wrongful conduct adversely affects the competitive conditions for the sale of oxymorphone hydrochloride extended release tablets by preventing the sale of oxymorphone hydrochloride extended release tablets by other potential suppliers, for example ASA, thereby enabling Penwest and Endo to unlawfully and unfairly limit the supply thereof.

106. As a direct result of Penwest and Endo's unfair and injurious conduct, ASA has been prevented from offering oxymorphone hydrochloride extended release tablets for sale.

107. Penwest and Endo's unfair conduct has caused and/or will cause the FDA to delay approval of ASA's ANDA.

108. Specifically, in order to trigger a 30 month stay on the FDA's approval of an ANDA, the NDA holder must, among other things, bring an infringement action against the ANDA filer asserting an Orange Book listed patent. 21 U.S.C. § 355(j)(5)(B)(iii).

109. Only by late-listing the '933 and '456 patents were Plaintiffs able to bring the instant infringement action and thereby secure a 30 month stay on the FDA's approval of ASA's ANDA.

110. But for the late-listing of the '933 and '456 patents—the '456 patent is the only patent Plaintiffs have asserted against ASA—Plaintiffs could not have reasonably initiated an infringement action against ASA to secure a 30 month stay of FDA approval of ASA's ANDA.

111. But for the late-listing of the '456 patent, Plaintiffs would not have had standing to assert the '456 patent against ASA.

112. On information and belief, the 30 month stay of the FDA's approval of ASA's ANDA will extend beyond the June 22, 2009 date on which Endo's regulatory exclusivity for OPANA ER® expires.

113. Not only did this unfair and injurious conduct cause injury to ASA by delaying FDA approval and ASA's entry into the marketplace, but also, as a direct result, ASA has been forced to defend itself in this action, incurring substantial damages in the form of legal costs and expenses.

114. Similarly, as a direct result of Penwest and Endo's unfair and injurious conduct, consumers have been precluded from benefiting by fair competition between and among suppliers of oxymorphone hydrochloride extended release tablets.

115. Penwest and Endo, unfairly and in bad faith, have acted in opposition to the principles of honesty and fair dealing, the rules of fair play and good conscience, and the

morality of the marketplace, and as such committed the commercially immoral acts complained of herein in violation of the common law of unfair competition of the State of New Jersey.

116. As a result, Penwest and Endo are unfairly able to extract artificially high prices for OPANA® ER without competition and without any fear of losing sales to competing products.

117. Penwest and Endo's conduct, which unfairly affected competition in selling oxymorphone hydrochloride extended release tablets, has caused irreparable damage and injury to ASA, and will continue to cause such injury unless Penwest and Endo's actions are enjoined. In response to Penwest and Endo's commercially immoral conduct which constitutes unfair competition and/or unfair methods of competition in violation of the common law of the state of New Jersey, ASA is entitled to preliminary and permanent injunctive relief, declaratory relief, and recovery of monetary damages.

PRAYER FOR RELIEF

WHEREFORE, ASA demands judgment in its favor and against Endo and Penwest as follows:

A. Granting ASA judgment in its favor on Plaintiff's Complaint;

B. Denying Penwest and Endo's request for injunctive relief;

C. Dismissing Penwest and Endo's Complaint with prejudice;

D. Declaring that claim 1 of the '143 patent is not and will not be infringed by ASA;

E. Declaring that claims 1 and 6 of the '933 patent are invalid;

F. Declaring that claim 6 of the '933 patent is not and will not be infringed by ASA;

G. Declaring that the claims of the '456 patent are invalid;

H. Declaring that the claims of the '456 patent are not and will not be infringed by ASA;

I. Declaring that claim 1 of the '250 patent is not and will not be infringed by ASA;

J. Declaring the claims of the '933 patent to be unenforceable;

K. Declaring the claims of the '456 patent to be unenforceable;

L. Finding this case to be exceptional under 35 U.S.C. § 285 and awarding ASA its costs and reasonable attorneys' fees;

M. Entering a permanent injunction enjoining Penwest and Endo from enforcing any patent against ASA in connection with ASA's extended release oxymorphone hydrochloride products, in view of Penwest and Endo's unclean hands;

N. Entering preliminary and permanent injunctions prohibiting Penwest and Endo from engaging in unfair competition and/or unfair methods of competition, including the acts complained of herein;

O. Directing an accounting to determine any and all of Penwest and Endo's profits and ASA's losses resulting from Penwest and Endo's activities and that any such losses be paid over to ASA and increased as the Court finds to be just under the circumstances of this case;

P. Awarding ASA compensatory damages for its injuries caused by Penwest and Endo's unfair competition and/or unfair methods of competition;

Q. Disgorging Penwest and Endo's profits collected due to their unfair competition and/or unfair methods of competition;

R. Awarding ASA punitive damages due to Penwest and Endo's unfair competition and/or unfair methods of competition;

S. Awarding ASA its costs and reasonable attorneys' fees due to Penwest and Endo's unfair competition and/or unfair methods of competition; and

T. Awarding any other such relief as is just and proper.

DEMAND FOR JURY TRIAL

Pursuant to the Federal Rule of Civil Procedure 38(b), ASA hereby demands a trial by jury as to all issues so triable.

Respectfully submitted,

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: August 14, 2008

By: /s/ Arnold B. Calmann

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Adam V. Floyd (afloyd@velaw.com)
Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

LOCAL CIVIL RULE 11.2 CERTIFICATION

Under Local Civil Rule 11.2, the undersigned counsel for ASA hereby certifies that this matter is not the subject of any other action asserted by ASA in any court, or of any pending arbitration or administrative proceeding. Another action is pending, however, with related subject matter, similar or identical claims and counterclaims, and identical parties: *Endo Pharmaceuticals, Inc. and Penwest Pharmaceuticals Co., v. Actavis South Atlantic LLC*, No. 08-1563 (KSH) (PS) (D.N.J. filed March 28, 2008).

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: August 14, 2008

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Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
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Stephen M. Hash (shash@velaw.com)
Reese P. McKnight (rmcknight@velaw.com)
Stephen C. Stout (sstout@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

LOCAL CIVIL RULE 201.1 CERTIFICATION

Under Local Civil Rule 201.1, the undersigned counsel for ASA hereby certifies that ASA seeks declaratory relief, and therefore this action is not appropriate for compulsory arbitration.

SAIBER LLC
Attorneys for Defendant and
Counterclaim Plaintiff
Actavis South Atlantic LLC

Dated: August 14, 2008

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SAIBER LLC
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VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

Attorneys for Defendant and Counterclaim Plaintiff
Actavis South Atlantic LLC

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. ACTAVIS SOUTH ATLANTIC LLC, Defendant.	**Civil Action No. 08-3482 (KSH) (PS)** **PLAINTIFFS' STATEMENT UNDER FEDERAL RULE OF CIVIL PROCEDURE 7.1(a)** ***DOCUMENT FILED ELECTRONICALLY***

Pursuant to Rule 7.1(a) of the Federal Rules of Civil Procedure, Actavis South Atlantic LLC hereby states as follows: Actavis, Inc. is the parent corporation of Actavis South Atlantic LLC. No publicly-held corporation owns more than 10% of the stock of Actavis South Atlantic LLC.

SAIBER LLC

Dated: August 14, 2008

By: /s/ Arnold B. Calmann

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

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Stephen C. Stout (sstout@velaw.com)
VINSON & ELKINS, L.L.P.
2801 Via Fortuna, Suite 100
Austin, Texas 78701
Telephone: (512) 542-8504
Facsimile: (512) 236-3278

Attorneys for Defendant and Counterclaim Plaintiff Actavis South Atlantic LLC

Arnold B. Calmann (abc@saiber.com)
Jakob B. Halpern (jbh@saiber.com)
SAIBER LLC
One Gateway Center, 13th Floor
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

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Stephen M. Hash (shash@velaw.com)
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VINSON & ELKINS, L.L.P.
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Telephone: (512) 542-8504
Facsimile: (512) 236-3278

Attorneys for Defendant and Counterclaim Plaintiff
Actavis South Atlantic LLC

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. ACTAVIS SOUTH ATLANTIC LLC, Defendant.	**Civil Action No. 08-3482 (KSH) (PS)** **CERTIFICATE OF SERVICE** ***DOCUMENT FILED ELECTRONICALLY***

ARNOLD B. CALMANN hereby certifies as follows:

I am an attorney-at-law of the State of New Jersey and a member of the firm of Saiber LLC, attorneys for defendant and counterclaimant Actavis South Atlantic LLC ("ASA") in the above matter. I hereby certify that, on this 14th day of August, 2008, I caused copies of ASA's Answer, Separate Defenses, Counterclaims and Demand for Jury trial to be served on the

following counsel of record by ECF and E-Mail:

Robert D. Rhoad (robert.rhoad@dechert.com)
Thomas P. Lihan (thomas.lihan@dechert.com)
DECHERT LLP
Princeton Pike Corporate Center
997 Lenox Drive
Building 3, Suite 210
Lawrenceville, NJ 08648-2317

Martin J. Black (martin.black@dechert.com)
George G. Gordon (george.gordon@dechert.com)
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808

Ann M. Caviani Pease (ann.pease@dechert.com)
DECHERT LLP
2440 W. El Camino Real
Suite 700
Mountainview, CA 94040-1499

/s/ Arnold B. Calmann
ARNOLD B. CALMANN

Dated: August 14, 2008

EXHIBIT F

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS, INC.,	
Plaintiff,	**Civil Action No. 08-1563(KSH)** **08-3482(KSH)**
v.	**ORDER ON INFORMAL APPLICATION &__ AMENDED PRETRIAL SCHEDULING ORDER**
ACTAVIS SOUTH,	
Defendant	

THIS MATTER having come before the Court for a telephone status conference on the record on August 14, 2008; and the parties advising the Court of the status of discovery and the filing of an action that deals with a different formulation/dosage of the same product; and the parties agreeing to the consolidation of these cases; and it appearing that there common issues of law and fact and that consolidation will avoid duplication and conserve the resources of the parties and the Court; and it appearing that while time may be needed to permit the parties to serve additional interrogatories and document demands directed to the allegations in the new complaint, the consolidation does not necessitate extension of the previously set pretrial deadlines; and for the reasons discussed during the telephone conference; and for good cause shown,

IT IS on this 14th day of August, 2008,

ORDERED that Civil Action No. 08-3482 shall be consolidated with Civil Action No. 08-1563 for all purposes; and

IT IS FURTHER ORDERED THAT:

1. The parties shall submit a discovery confidentiality order and certification as required by Local Civ. R. 5.3 no later than **deadline passed.** The discovery confidentiality Order dated June 26, 2008 shall govern both cases.

2. The request for leave to file a motion to dismiss in lieu of a response to the counterclaim directed at the '143 patent is denied as moot as the obligation to respond to this portion of the counterclaim is stayed until September 22, 2008. If the patent expires on or before that date, then the parties shall submit a letter and proposed form of Order to the United States District Judge dismissing as moot this portion of the counterclaim. Nothing herein precludes discovery about the '143 patent;

3. The plaintiff shall file a response to the other portions of the Counterclaim no later than **deadline passed.**

4. No proceedings, including discovery, will be stayed while dispositive motions or Markman issues are pending;

5. No later than **deadline passed**, the plaintiffs shall identify the claims of the '456 patent that they contend the defendant infringes. Any supplementation needed as a result of the allegations embodied in Civil Action No. 08-3482 shall be disclosed no later than **September 12, 2008**;

6. No later than **deadline passed**, the plaintiffs shall provide the factual basis for their assertion that the defendant infringes the identified claims of the patent. Any supplementation needed as a result of the allegations embodied in Civil Action No. 08-3482 shall be disclosed no later than **September 12, 2008**;

7. No later than **deadline passed**, the defendant shall provide the factual basis for its assertion that the '456, 933, and '920 patents are invalid, including citations to prior art. Any supplementation needed as a result of the allegations embodied in Civil Action No. 08-3482 shall be disclosed no later than **September 12, 2008**;

8. No later than **October 3, 2008**, the parties shall exchange proposed claims terms and claims construction;

9. No later than **October 30, 2008,** the parties shall submit their joint claims construction chart;

10. Opening Markman briefs shall be submitted no later than **November 24, 2008**. Responsive Markman briefs shall be submitted no later than **December 18, 2008**. Judge Hayden shall advise the parties if she seeks a tutorial or needs oral argument.

IT IS FURTHER ORDERED THAT:

I. COURT DATES

1. There shall be telephone status conferences as follows:

Date of Call	Party to Initiate
October 29, 2008 at 1:00 p.m.	**Defendant**
January 13, 2009 at 1:00 p.m.	**Plaintiff**
April 14, 2009 at 1:00 p.m.	**Defendant**

2. There will be a settlement conference before the undersigned on **TO BE SET. Five (5) business days** before the conference, each party should submit a confidential memorandum to the Court, not to exceed 5 pages, summarizing the relevant facts, the respective legal positions,

status of the case, and the client's position on settlement. Trial Counsel and clients with full settlement authority must attend the conference. If the trial counsel **and** client with full settlement authority do not appear, the settlement conference may be cancelled or rescheduled and the noncompliant party and/or attorney may be sanctioned, which may include an assessment of the costs and expenses incurred by those parties who appeared as directed.

3. A final pretrial conference shall be conducted pursuant to Fed. R. Civ. P. 16(d) on **September, 8, 2009 at 10:00 a.m.** The Final Pretrial Conference will occur even if there are dispositive motions pending. The Court will adjourn the Final Pretrial conference only if the requesting party makes a compelling showing that manifest injustice would otherwise result absent adjournment.

II. DISCOVERY AND MOTION PRACTICE

4. Fed. R. Civ. P. 26 disclosures are to be exchanged on or before **completed.**

5. Discovery necessary to engage in meaningful settlement discussions: **none.**

6. A. The parties may serve interrogatories limited to **25** single questions including subparts and requests for production of documents directed to the claims/defenses in Civ. No. 08-1563 on or before **deadline passed,** which shall be responded to no later than **deadline passed.**

B. The parties may serve interrogatories limited to **25** single questions including subparts and requests for production of documents directed to the claims/defenses in Civ. No. 08-3482 on or before **September 5, 2008,** which shall be responded to no later than **October 6, 2008.**

B. Foreign evidence collection shall commence no later than **deadline passed.**

C. Final supplemental responses to contention interrogatories shall be provided no later than **February 8, 2009. Additional supplementation may also be made no later than ten business days after the date of the Order resolving claims construction;**

7. The number of depositions to be taken by each side shall not exceed **10**. No objections to questions posed at depositions shall be made other than as to lack of foundation, form or privilege. See Fed. R. Civ. P. 32(d) (3) (A). No instruction not to answer shall be given unless a privilege is implicated. The depositions shall be completed no later than **March 1, 2009**.

8. Fact discovery is to remain open through **March 1, 2009**. No discovery is to be issued or engaged in beyond that date, except upon application and for good cause shown.

9. Counsel shall confer in a good faith attempt to informally resolve any discovery disputes before seeking the Court's intervention. Should such informal effort fail to resolve the dispute, the matter shall be brought to the Court's attention via a joint letter that sets forth: (a) the request, (b) the response; (c) efforts to resolve the dispute; (d) why the complaining party believes the information is relevant and why the responding party's response continues to be deficient; and (e) why the responding party believes the response is sufficient. No further submissions regarding the dispute may be submitted without leave of Court. If necessary, the Court will thereafter schedule a telephone conference to resolve the dispute.

No discovery motion or motion for sanctions for failure to provide discovery shall be made before utilizing the procedures set forth in these paragraphs without prior leave of Court.

Any unresolved discovery disputes (other than those that arise during depositions) must be brought before the Court no later than **November 10, 2008** and the Court will not entertain applications concerning discovery matters, informally or otherwise, after this date.

10. Any motion to amend pleadings or join parties must be filed by **December 1, 2008.**

11 All dispositive motions shall be discussed in advance of filing with the undersigned either in person or by teleconference.

If leave is granted to file a summary judgment motion, the following protocol shall apply:

a. Each motion for summary judgment shall be supported by a separate, short, and concise statement of material facts, set forth in numbered paragraphs, as to which the moving party contends there is no genuine issue of material fact to be tried. Each fact asserted in the statement shall be supported by a record citation. A "record citation" is a citation to a specific page or paragraph of identified record material supporting the assertion.

b. Each response in opposition shall be accompanied by a separate, short, and concise statement of material facts. The opposing statement shall admit, deny or qualify the facts by reference to each numbered paragraph of the moving party's statement of material facts and unless a fact is admitted, shall support each denial or qualification by a record citation. The opposing statement may contain in a separate section additional facts, set forth in separate numbered paragraphs and supported by a record citation.

c. In the event a party seeks to submit a reply, the party shall file a formal request for permission to do so within the time period provided by Local Rule, attaching the proposed reply. Accompanying the proposed reply shall be a separate, short, and concise statement of material facts which shall be limited to any additional facts submitted by the opposing party. The reply statement shall admit, deny or qualify such additional facts by reference to the numbered paragraphs of the opposing party's statement of material facts, and unless a fact is admitted, shall support each denial or qualification by a record citation.

d. Facts contained in a supporting or opposing statement of material facts, if supported by record citations, shall be deemed admitted unless properly controverted. The Court may disregard any statement of fact not supported by a specific citation to record material properly considered on summary judgment. The Court shall have no independent duty to search or consider any part of the record not specifically referenced in the parties' separate statement of facts.

e. Local Rules governing electronic filing and length, font-size, and format of moving, opposing and reply briefs shall continue to apply as appropriate. Parties shall provide the Court with two hard copies of all submissions by delivering same to the Clerk's Office, Attention Judge Katharine Hayden.

III. EXPERTS

12. All affirmative expert reports shall be delivered by **May 1, 2009.**

13. All responding expert reports shall be delivered by **June 30, 2009**.

14. a. All expert reports are to be in the form and content as required by Fed. R. Civ. P. 26(a) (2)(B). No expert shall testify at trial as to any opinions or base those opinions on facts not substantially disclosed in the experts report.

b. All expert depositions shall be completed by **July 30, 2009**.

IV. FINAL PRETRIAL CONFERENCE

15. A final pretrial conference shall be conducted pursuant to Fed. R. Civ. P. 16(d) on **September, 8, 2009 at 10:00 a.m.**. The Final Pretrial Conference will occur even if there are dispositive motions pending. The Court will adjourn the Final Pretrial conference only if the requesting party makes a compelling showing that manifest injustice would otherwise result absent adjournment.

16. Not later than **20 working days** before the pretrial conference, the parties shall exchange copies of all proposed trial exhibits. Each exhibit shall be pre-marked with an exhibit number conforming to the party's exhibit list.

17. All counsel are directed to assemble at the office of Plaintiff's counsel not later than **ten (10) days** before the pretrial conference to prepare the proposed Joint Final Pretrial Order in the form and content required by the Court. Plaintiff's counsel shall prepare the Joint Pretrial Order and shall submit it to all other counsel for approval and execution.

18. With respect to non-jury trials, each party shall submit to the District Judge and to opposing counsel proposed Findings of Fact and Conclusions of Law, trial briefs and any hypothetical questions to be put to an expert witness on direct examination.

19. The original joint proposed final pretrial order shall be delivered to the CHAMBERS of the undersigned no later than **September 1, 2009 at 4:00 p.m.** All counsel are responsible for the timely submission of the Order.

20. The Court expects to engage in meaningful settlement discussions at the final pretrial conference. Therefore, trial counsel who actually has full settlement authority must attend the conference and clients or other persons with full settlement authority must be available by telephone.

V. MISCELLANEOUS

21. The Court may from time to time schedule conferences as may be required, either sua sponte or at the request of a party.

22. Since all dates set forth herein are established with the assistance and knowledge of counsel, there will be no extensions except for good cause shown and by leave of Court, even with consent of all counsel.

23. A copy of every pleading, document or written communication with the Court shall be served on all other parties to the action. Any such communication which does not recite or contain a certification of such service may be disregarded by the Court.

24. Communications to the Court by facsimile will not be accepted. All communications to the Court shall be in writing or by telephone conference.

25. **FAILURE TO COMPLY WITH THE TERMS OF THIS ORDER MAY RESULT IN SANCTIONS.**

s/Patty Shwartz
UNITED STATES MAGISTRATE JUDGE